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Dissertation

THE REACTIONS OF MORPHOLINE AND FORMALDEHYDE WITH ORGANIC COMPOUNDS WHICH CONTAIN AN ACTIVE HYDROGEN ATOM

by

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INTRODUCTION

In recent years the development of new amines has been outstanding. One of the new products is morpholine, a fairly cheap cyclic aliphatic secondary amine. Morpholine was discovered in 1889 by Knorr who prepared it by the action of 70 percent sulfuric acid on diethanolamine. From 1889 to 1935, however, morpholine received little attention since it was not readily available. In 1935, commercial production became a reality based upon patents utilizing β,β'-dihalogenoethyl ethers and ammonia. Wilson (54) already has reviewed the literature on morpholine until 1935. Since then papers have been appearing with increasing regularity.

In 1936 Bruson (5) (6) described the preparation of morpholinomethyl phenols. He condensed phenols which had at least one readily replaceable nuclear hydrogen atom with at least one molecular equivalent each of morpholine and formaldehyde. He claimed that the morpholinomethyl group entered the benzene nucleus ortho to the OH group. This work suggested the problem of substituting aliphatic alcohols for the aromatic polyhydroxy compounds. Since the reaction involves the preparation of the intermediate hydroxymethyl morpholine which is unstable, it seemed likely that any compound with an active hydrogen atom might condense with this compound. Thus the problem was extended to include the reaction of morpholine and formaldehyde with alcohols, ketones, ortho and para nitrotoluenes, hydrochloric acid, aliphatic nitro

compounds, amines, nitriles and malonic ester.

I. THE REACTION OF MORPHOLINE, FORMALDEHYDE AND ALIPHATIC ALCOHOLS.

Introduction

Dialkylaminomethyl alkyl ethers have been prepared by MaLeod and Robinson (42) by the condensation of secondary amines with 37 percent aqueous formaldehyde and various alcohols. Robinson and Robinson (46) later used the same procedure for the first step in the preparation of tertiary amines of the form $RCH_2NR'R''$.

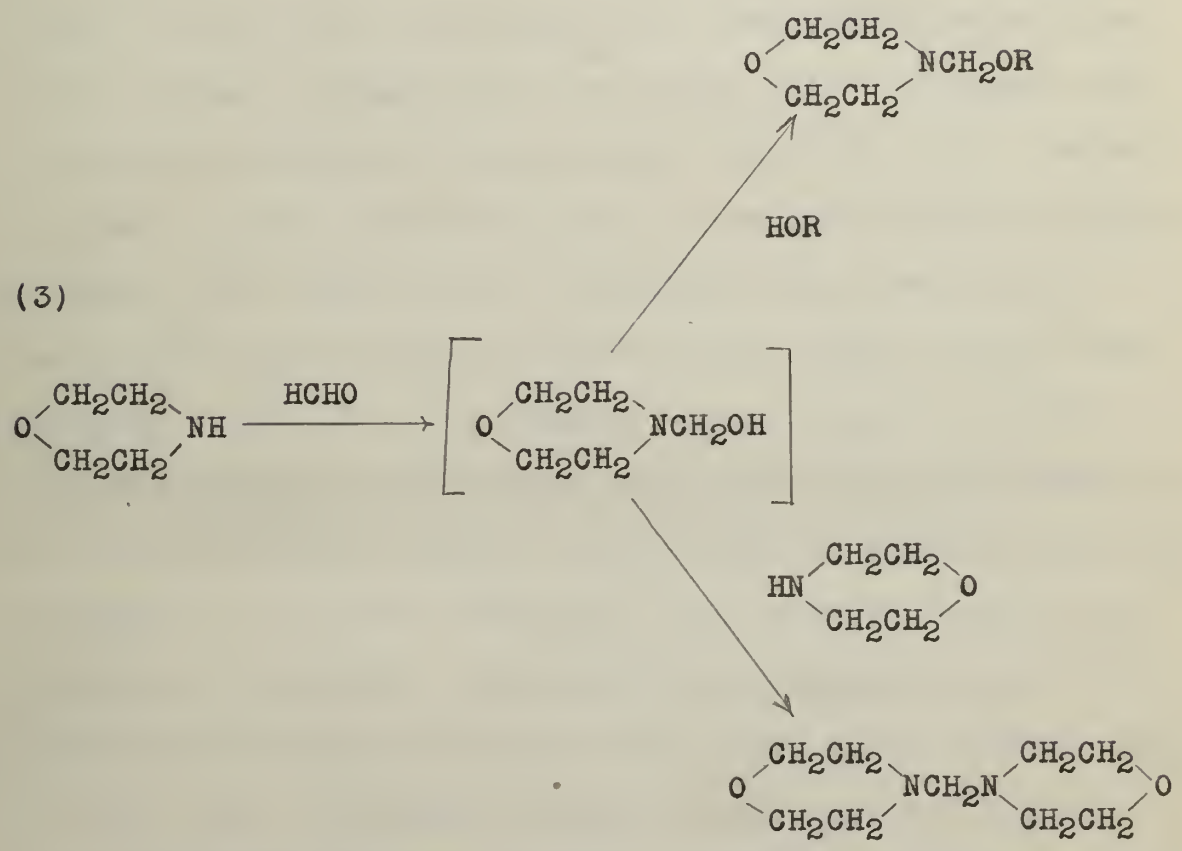
$$(1)\ R'R''NH + CH_2O + C_4H_9OH \xrightarrow{K_2CO_3} R'R''NCH_2OC_4H_9 + H_2O$$

$$(2)\ R'R''NCH_2OC_4H_9 + RMgCl \longrightarrow R'R''NCH_2R + C_4H_9OMgCl$$

The methyl alcohol in the 37 percent commercial formaldehyde did not form any dialkylaminomethyl ethers because these substances are more easily hydrolyzed than similar ethers derived from higher alcohols (46). Stewart and Bradley (51) prepared dialkylaminomethyl methyl ethers by using paraformaldehyde in place of 37 percent commercial formaldehyde. In this thesis a series of 4-morpholinomethyl ethers is reported. Paraformaldehyde was used in place of aqueous formaldehyde in all reactions. Removal of water was accomplished by binary and ternary mixtures rather than by saturation of the reaction mixture with potassium carbonate.

The preparation of 4-morpholinomethyl ethers may be formulated as follows:

(3)



It will be seen from equation 3 that there are two reactions possible when the three reactants are mixed. In order to increase the yield of the ether, two equivalents of alcohol to one each of morpholine and formaldehyde were used.

Table I (Page 18) shows the percentage of morpholine converted into the 4-morpholinomethyl alkyl ether and the dimorpholinomethane, together with the boiling points, nitrogen analyses, and neutral equivalents. Increasing yields

of the ether were obtained with increasing molecular weight of the primary alcohols from methyl to n-propyl and n-butyl. This may be due to the fact that the ethers obtained from higher alcohols are hydrolyzed less easily than those from lower alcohols. Comparison of n-propyl with iso-propyl and n-butyl or iso-butyl with sec-butyl illustrates that primary alcohols produce a greater yield of the ether than secondary alcohols. The comparison of sec-butyl with tert-butyl in turn shows that secondary alcohols form larger yields than tertiary alcohols. These results may be taken as evidence that the hydrogen of the water split off during the formation of the ether comes from the alcohol and the hydroxyl from the hypothetical 4-morpholinemethanol. The results parallel the reactions of primary, secondary, and tertiary alcohols with sodium and the esterification with acids. Allyl alcohol seems to react like a secondary alcohol. Benzyl alcohol behaves like a typical aliphatic alcohol, forming the greatest yield of ether.

The methyl, ethyl, and sec-butyl ethers formed picrates which melted at 146-148°, the melting point of morpholine picrate. Mixtures of morpholine picrate and picrates of the ethers melted at 146-148°. All the picrates were morpholine picrate. The fact that 4-morpholinomethyl sec-butyl ether formed a picrate over-night and that 4-morpholinomethyl methyl ether formed a picrate immediately is in accord with the hydrolysis phenomena of the ethers. As the alcohol increases

in molecular weight, hydrolysis becomes more difficult (46).

A. PREPARATION OF 4-MORPHOLINOMETHYL ETHERS.

Preparation of materials:

Allyl alcohol: A technical grade of allyl alcohol (200 cc.) containing fifteen percent of water was saturated with potassium carbonate and allowed to stand for one hour. The water layer was then removed in a separatory funnel. The alcohol was dried over Drierite for one hour and distilled. The fraction boiling at 96-97° was collected.

All the alcohols, which were the best grade of Eastman Kodak products, were redistilled before use. The paraformaldehyde was also an Eastman Kodak product. The morpholine, a Carbide and Carbon Chemicals Corporation product, was distilled and that portion boiling at 126-128° was collected.

Formaldehyde: Formaldehyde is available as a gas, solution (formalin), or solid (paraformaldehyde). The commonly-used solution of formaldehyde is sold under the name "formalin," an aqueous solution containing methyl alcohol and not less than 37 percent by weight of formaldehyde. Paraformaldehyde, or trioxymethylene, is the solid form, a polymer obtained by the evaporation of an aqueous solution of formaldehyde. Any form can be used in the present reaction. The gas was eliminated because of the greater ease in working with a liquid or a solid. Formalin is not ideal for it contains water, one of the products of the reaction. Also since Robinson (46) has reported that methyl alcohol in formalin did not interfere in the preparation of butyl and higher ethers (because of

the ease of hydrolysis of the methyl ether formed) it is apparent that formalin is not suitable for the preparation of 4-morpholinomethyl methyl ether. Paraformaldehyde, on the other hand, is easy to handle and does not suffer from the presence of water. Stewart and Bradley (51) used it to prepare dialkylaminomethyl methyl ethers.

Drying agents: Robinson removed water by saturating the reaction mixture with potassium carbonate and allowing to stand over-night. The oil was then taken up in ether, dried over potassium carbonate and distilled. Stewart and Bradley (51) saturated the reaction mixture with potassium carbonate also. The potassium carbonate was filtered off with suction and the filtrate distilled. Each fraction was dried with sodium and refractionated. The ability of calcium sulfate to combine with water at high temperatures (44) suggested the possibility of saturating the reaction mixture with calcium sulfate and distilling directly. Since drying with the aid of a constant boiling mixture is theoretically more effective than drying with salts, binary and ternary mixture methods were used throughout, for this last method proved to be very efficient.

Experiment #1:

To a cooled solution of 41 grams of formalin and 37 grams of secondary butyl alcohol 43.5 grams of morpholine was added. The mixture was saturated with potassium carbonate, shaken vigorously, and put away over-night. The colorless oil

was removed, taken up in ether, and dried over anhydrous potassium carbonate. The ether was removed and the oil was distilled. Upon distillation at ordinary pressures, the oil decomposed. At 10 mm. the oil distilled gradually from 96-130° with no definite fractions. No analysis of the final product was attempted.

Experiment #2:

In a 500 cc. round-bottomed flask fifteen grams of paraformaldehyde (equivalent to 0.5 mole of formaldehyde) was mixed with 43.5 grams (0.5 mole) of morpholine. A reflux condenser was attached and 37 grams (0.5 mole) of secondary butyl alcohol was added slowly. The reaction mixture became warm. The mixture was saturated with potassium carbonate and put away over-night. The potassium carbonate was removed by suction filtration. The fraction boiling at 105-120° at 15 mm. was kept and dried over sodium. Upon refractionation 15.5 grams of a colorless oil boiling at 90-100° at 12 mm. was obtained.

Neutral Equivalent of Product: The oil (0.1940 grams) was dissolved in 10 cc. of 95 percent ethyl alcohol and a drop of methyl orange was added. An end-point was reached after 10.89 cubic centimeters of .1113N hydrochloric acid was added.

$$.0001113 \times 10.89 = \frac{.1940}{X}$$

$$X = 160.1 \text{ neutral equivalent}$$

The theoretical neutral equivalent of 4-morpholinomethyl sec-

butyl ether is 173. The analysis indicated that the product was essentially the 4-morpholinomethyl sec-butyl ether but impurities were present. The improvement over the first method was very noticeable. At this point it was thought that the primary alcohols might react faster than secondary butyl alcohol, thus primary alcohols were used in the remainder of the preliminary experiments.

Experiment #3:

In a 500 cc. round-bottomed flask 43.5 grams of morpholine and 37 grams of n-butyl alcohol were mixed together. Fifteen grams of paraformaldehyde was added. The flask was connected to a reflux condenser and was shaken. The mixture was refluxed for one-half hour. Drierite (30 grams) was added and the mixture was refluxed again for one-half hour. After twenty hours a sample of the oil was tested with sodium. A vigorous reaction occurred. At this point the experiment was stopped as it was clear that the Drierite had not absorbed enough water. Since 0.5 mole of each reactant was used, 9 cc. was the maximum amount of water present. Morton (44) states that Drierite absorbs only 6.6 percent of water per weight of Drierite used. Thus about 150 grams of drying agent was actually needed. The large amount of Drierite necessary eliminated this method from further consideration.

Experiment #4:

In this experiment the effect of refluxing the reaction mixture and the nature of the final fractions were investigated.

Fifteen grams of paraformaldehyde, 43.5 grams of morpholine, and 30 grams of n-propyl alcohol were mixed together and heated under reflux for three hours. The mixture was worked up as described in the second experiment. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	81-85	10	14.4	159.9
II	85-114	10	4.3	142
III	114-116	8	10.1	87.9

Fraction I corresponds to the 4-morpholinomethyl n-propyl ether (theoretical neutral equivalent is 159). Fraction III suggested dimorpholinomethane, the neutral equivalent of which is 93. Fraction II would thus be a mixture of the two compounds. In order to verify the composition of fraction III pure dimorpholinomethane was prepared.

Experiment #5:

Fifteen grams of paraformaldehyde and 87 grams of morpholine were mixed together. The mixture was heated on a steam-bath for two hours under reflux, cooled, and saturated with anhydrous potassium carbonate. A great deal of heat was liberated upon the addition of the potassium carbonate. The potassium carbonate was removed by suction filtration. The filtrate was dried with sodium and fractionated. A forerun of morpholine was distilled first. At 120-122° at 10 mm., 38.7 grams of a colorless oil distilled. The yield of dimorpholinomethane was 41.6 percent. Dimorpholinomethane formed a picrate melting at 147-148.5°.

Analysis of Product:

Neutral equivalent: Theoretical 93.0

Found 93.2

Kjeldahl: Calculated for $C_9H_{18}N_2O_2$ N = 15.05

Found N = 15.13

Experiment #6:

In this experiment morpholine was added slowly at 100°. Since the boiling points of water and morpholine are so far separated from dimorpholinomethane, it was thought that a separation of the final product could be effected by efficient fractionation without the use of drying agents.

To fifteen grams of paraformaldehyde at 100° was added 87 grams of morpholine. The addition took one hour. The reaction mixture was then fractionated without further treatment by means of a 24-inch, insulated, "Vigreuxed" column. The fraction distilled up to 121° at 10 mm. was discarded. At 121-122° at 10 mm., 81.9 grams of a colorless oil was collected. The yield was 88 percent.

During the course of this work, Harradence and Lions (25) reported the preparation of dimorpholinomethane from formalin. A colorless oil boiling at 139-140° at 29 mm. was obtained. They also reported the 4-morpholinomethyl n-butyl and iso-propyl ethers prepared by the method of Robinson and Robinson (46). They encountered difficulties in separating the ethers from dimorpholinomethane. A refractionated n-butyl

ether fraction had an equivalent weight of 162 (theoretical equivalent weight is 173). It is surprising to note that the n-butyl ether was distilled at ordinary pressures at 218-222°. In the experiments described equimolecular weights of morpholine and the alcohol were used.

In order to prepare higher yields of ether, an excess of alcohol was used in all further experiments. Morpholine was added slowly to the alcohol and paraformaldehyde so that an excess of alcohol was always present. The success of the experiment led to attempts at drying by binary and ternary mixtures.

Experiment #7:

Fifteen grams of paraformaldehyde (0.5 mole of formaldehyde) and 23 grams (0.5 mole) of absolute ethyl alcohol were placed in a 500 cc. three-necked flask which was fitted with a mercury-sealed mechanical stirrer, a separatory funnel, and a reflux condenser. A mixture of 43.5 grams (0.5 mole) of morpholine and 23 grams (0.5 mole) of absolute ethyl alcohol was added in the course of an hour. After the addition, the reaction mixture was heated on a steam-bath for one hour. The mixture was transferred to a 500 cc. round-bottomed flask, 100 cc. of benzene was added, and the mixture was distilled. The ternary mixture of water, benzene and alcohol distilled at 65° (34). The fraction up to 79° was distilled at ordinary pressure. At 7 mm. the fraction boiling up to 59° was discarded. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	59-64	7	20.5	145.7
II	64-97	7	13.4	140.6
III	97-125	7	17.5	107.4

Fraction I is pure 4-morpholinomethyl ethyl ether, while Fraction III consists chiefly of dimorpholinomethane. Fraction II is a mixture of the two.

Experiment #8:

In the previous experiment the ternary mixture took out the water after the reaction had been completed. If, however, water were removed during the reaction, more ether should be formed.

Fifteen grams of paraformaldehyde, 23 grams (0.5 mole) of absolute ethyl alcohol, and 100 cc. of dry benzene were placed in a 500 cc. three-necked flask which was equipped with a mercury-sealed mechanical stirrer, a separatory funnel, and a fractionating column attached to a condenser for distilling the ternary mixture. The flask was heated in a water-bath kept at 85°. A mixture of 43.5 grams of morpholine and 23 grams (0.5 mole) of absolute ethyl alcohol was dropped slowly into the reaction mixture which was stirred continuously. During this addition, which was completed in an hour, the ternary mixture of water, alcohol, and benzene distilled at 65°. After all the morpholine was added the temperature of the water-bath was raised to 100° and the remaining benzene distilled off with the alcohol. The residue was transferred to a 500 cc.

round-bottomed flask to which was attached an efficient fractionating column. The distillate which came over up to 58° at 6mm. was discarded. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	58-63	6	26.7	144.8
II	63-110	6	24.3	120.5
III	110-113	6	4.1	97.3

Fraction I is pure 4-morpholinomethyl ethyl ether (neutral equivalent of 145) while fraction III consists chiefly of dimorpholinomethane (neutral equivalent of 93). If we make the reasonable assumption that fractions II and III are mixtures of the ether and dimorpholinomethane, it is then possible to determine the amount of each component from the titration data and simultaneous equations. For example, 0.2546 grams of fraction II required 20.71 cc. of 0.1024N hydrochloric acid for neutralization (methyl orange end-point). One gram of 4-morpholinomethyl ethyl ether requires 68.36 cc. of this acid and one gram of dimorpholinomethane requires 104.98 cc. of this acid for neutralization. Solving the simultaneous equations:

$$x + y = 0.2546$$

$$68.36x + 104.98\,y = 20.71$$

$x = 0.1641$. Therefore 64.5 percent of fraction II is the 4-morpholinomethyl ethyl ether. This type of analysis was used in all subsequent experiments to determine the percentage of morpholine converted to the ether and dimorpholinomethane

reported in Table I.

Experiment #9:

In this experiment all of the alcohol was mixed with the paraformaldehyde so that a greater excess of alcohol was present at any time. All the other details of the previous experiment were retained.

Fifteen grams of paraformaldehyde, 46 grams of absolute ethyl alcohol, and 100 cc. of dry benzene were mixed together. Morpholine (43.5 grams) was added slowly with no diluent. The product was worked up as described in experiment #8. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	62-67	9	24.9	144.5
II	67-119	9	21.9	-

Fraction II was not analyzed as the main object of this experiment was the comparison of the pure ether fraction with that in the previous experiment. Since no improvement in yield was attained, this procedure was discarded.

Experiment #10:

The effect of the reaction time on the yield of the 4-morpholinomethyl methyl ether was investigated. It seemed that the yield of ether might be diminished by hydrolysis if the reaction time were extended since dialkylaminomethyl ethers of low molecular weight are considered more easily hydrolyzed than the higher homologues.

To fifteen grams of paraformaldehyde and 16 grams of methyl alcohol was added a mixture of 43.5 grams of morpholine

and 16 grams of methyl alcohol. The external bath was kept at 75-80°. After the addition the reaction mixture was cooled, transferred to a 500 cc. round-bottomed flask, and fractionated. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	55.6-57	8	20.0	131.9
II	57-113	8	8.8	127.7
III	113-120	8	18.1	96.1

The experiment was repeated but after addition of the morpholine, the reaction was refluxed eight hours. The following fractions were collected.

Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equivalent
I	51-53	6	13.7	132.0
II	53-113	6	12.1	128.5
III	113-118	6	19.3	96.4

The results indicated that the yield of ether was lessened by extended refluxing.

Summary: The use of binary and ternary mixtures for drying proved to be the most convenient method for the preparation of 4-morpholinomethyl ethers. The yields were increased and the working time was reduced. The yield of low molecular weight ethers was reduced by extended refluxing. All the 4-morpholinomethyl alkyl ethers described in Table I were made by the method given in experiment #8, with the given modifications in the footnotes of Table II, which gives the summary of all the experimental data.

TABLE I

Alcohol	% Morpholine converted to ether	% Morpholine converted to dimorpholino-methane	B.p. of ether °C.	Mm.	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	46.2	35.5	55.6-57	8	131	131.9	10.68	10.58
Ethyl	59.3	26.2	58-63	6	145	144.8	9.66	9.64
n-Propyl	74.0	12.0	100-102	22	159	158	8.81	8.80
Isopropyl[a]	29.7	53.6	64-66	6	159	158	8.81	8.89
n-Butyl[a]	73.8	16.3	99.5-100.5	11	171	171	8.09	8.22
Isobutyl	68.0	17.2	90.5-92.5	10	171	172	8.09	8.12
s-Butyl	58.9	34.0	92-94	10	171	170.5	8.09	8.25
t-Butyl	9.4	75.4						
Allyl	52.4	36.3	82-83	7	157	156.6	8.92	8.93
Benzyl	76.8	4.4	152-154	7	207	206	6.76	6.83

[a] Harradence and Lions, J. Proc. Roy. Soc. N.S. Wales, 73, 22 (1939).

Table II

Alcohol used and temp. of external bath, °C.	Fraction	B.p., °C.	Mm.	Weight, grams	Neutral Equival.
Methyl[a] 75-80	I	55.6-57	8	20.0	131.9
	II	57-113	8	8.8	127.7
	III	113-120	8	18.1	96.1
Propyl 87-92	I	100-102	22	40.9	158
	II	102-128	22	12.7	152
	III	128-131	22	10.7	120
Isopropyl 80-85	I	89-93	21	3.9	155
	II	93-98	21	5.8	155
	III	98-129	21	5.7	144
	IV	129-135	21	33.1	105
n-Butyl[a] 100	I	99.5-100.5	11	30.8	171
	II	100.5-104	11	14.5	166
	III	104-110	11	8.8	158
	IV	110-122	11	17.3	134
Isobutyl[a] 100	I	90.5-92.5	10	29.9	172
	II	92.5-97.5	10	15.1	170
	III	97.5-116	10	8.2	145
	IV	116-121	10	13.7	126
s-Butyl[a] 100	I	92-94	10	10.3	170.5
	II	94-100	10	17.0	165
	III	100-117	10	12.7	151
	IV	117-122	10	26.8	123
t-Butyl[a] 100	I	112-120	11	7.8	111
	II	120-123	11	16.0	102
	III	123-125	11	19.5	98
Allyl[a,b] 100	I	82-83	7	10.8	156.6
	II	83-88	7	12.3	153.4
	III	88-111	7	11.9	134.9
	IV	111-116	7	23.0	111.3
Benzyl[a,b] 100	I	140-146	7	6.5	173
	II	146-152	7	10.8	187.4
	III	152-154	7	64.0	206

[a] No benzene used. Mixture was fractionally distilled after addition of morpholine was complete. First fraction was a binary mixture of the alcohol and water.

[b] 0.75 mole of alcohol was used.

Formation of Picrates:

Four drops of the ether were added to 15 cc. of 95 percent ethyl alcohol saturated with picric acid. The solution was heated to boiling on a steam-bath and allowed to cool slowly. The crystals were filtered off, dried, and then recrystallized from 95 percent ethyl alcohol.

Table III

Picrate from	Melting Point
4-Morpholinomethyl methyl ether	146.1-148°
4-Morpholinomethyl sec-butyl ether	146.2-148°
Morpholine	146.5-148°
Mixed melting points of picrates from	
4-Morpholinomethyl methyl ether and morpholine	146.5-148°
4-Morpholinomethyl s-butyl ether and morpholine	146.5-148°
4-Morpholinomethyl s-butyl ether and methyl ether	146.2-148°

Table III shows clearly that all the picrates were morpholine picrate formed by the hydrolysis of the ethers. Picrates were then prepared by substituting dry benzene saturated with picric acid in place of the ethyl alcohol. It was thought that less hydrolysis would occur in benzene. Picrates came down from alcoholic solution immediately or at most six hours, but standing in an ice-box for three or four days was necessary before crystals formed in benzene solution. The picrates were recrystallized from absolute ethyl alcohol. The allyl, iso-propyl, and sec-butyl ethers yielded picrates melting, as before, at 146-148°.

Analysis of 4-morpholinomethyl iso-propyl ether picrate.

Kjeldahl:	Theoretical	N = 14.53
	Found	N = 17.84
	Morpholine picrate	N = 17.75

Procedure for a Kjeldahl determination on picrates (49): The picrate (0.3 grams) is placed in a Kjeldahl flask and treated with 30 cc. of concentrated sulfuric acid to which one gram of salicylic acid has been added. Shake and let stand for five minutes. Then add five grams of sodium thiosulfate and heat for five minutes. After cooling add ten grams of sodium sulfate and a few crystals of copper sulfate and treat in the usual manner.

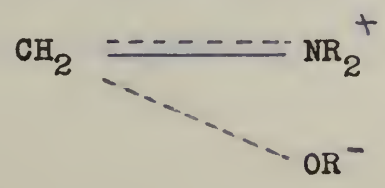
It was considered impossible to make the picrates in the usual manner. Unsuccesful attempts to make a satisfactory solid derivative of diethylaminomethyl β-ethoxyethyl ether have been reported. In all cases (hydrochloride, ethyl iodide, and picrate) hydrolysis occurred. It is interesting to note the effect of an additional CH_2 group. Morpholinoethyl ethers are much more stable and their picrates have been reported (40) (41).

Discussion

The formation of picrates shows that the ethers are very easily hydrolyzed. In organic compounds the ease of hydrolysis rises to a maximum where the polarity differentiation is the greatest. When a compound becomes less polar, it is less easily hydrolyzed. When a compound AB on hydrolysis yields AH and BOH, A must be electronegative and B must be electropositive. To account for the hydrolysis phenomena of the ethers Robinson and Robinson (46) considered the following equilibrium:

$$R_2NCH_2OR \rightleftharpoons (CH_2{=}NR_2)^+ + OR^-$$

They discarded this equilibrium and possible existence of any ammonium alkyloxide since the ethers can be distilled without decomposition. They preferred to represent the high reactivity to hydrolysis by the formula



The formula represents a partial intramolecular electrovalency connecting the N and O atoms. The formula indicates that the ease of hydrolysis is connected with the "onium" tendencies of the nitogen atom. In the following comparison

$$R_2NCH_2OR + R'MgX \longrightarrow \text{Vigorous reaction}$$

$$ROCH_2OR + R'MgX \longrightarrow \text{Unaffected}$$

the great reactivity of the amino ether is ascribed to the polarization of the molecule effected by the "onium" tendency of the nitrogen atom. A polarized molecule is expected to react with the Grignard reagent because of the electropositive character of the magnesium. On this basis all compounds which react with Grignard reagents are polarized.

The ethers are rapidly hydrolyzed in one equivalent of acid. The equation may be formulated as follows:

$$R_2NCH_2OR + H^+ + H_2O \longrightarrow R_2NH_2^+ + CH_2O + HOR$$

Robinson's formula above predicts that the separation of the alkoxyl group precedes the rupture of the carbon-nitrogen linkage. Stewart and Bradley (52) attempted to show that the iminium ion is an intermediate in the separation of the carbon and nitrogen atoms.

$$R_2NCH_2OR + H^+ \longrightarrow R_2\overset{+}{N}H{-}CH_2OR \longrightarrow \underset{\text{iminium ion}}{R_2\overset{+}{N}{=}CH_2} + ROH$$

Stewart and Bradley rapidly neutralized diethylaminomethyl iso-butyl ether to a methyl orange end-point with 1N hydrochloric acid. The solution was then evaporated in a vacuum over calcium chloride. In one experiment $CH_2{=}N(C_2H_5)_2Cl\cdot 6H_2O$ was isolated. Although this experiment was repeated many times, the product was never again obtained.

When a slightly acid solution of the ether is treated with alkali, the iminium ion reacts as follows:

$$R_2\overset{+}{N}{=}CH_2 + OH^- \longrightarrow R_2NCH_2OH$$

In dilute solutions the amino alcohol corresponds at equilibrium to 80 percent of the theoretical amount. Upon acidification the amino alcohol can react in two ways:

$$R_2NCH_2OH + H^+ \longrightarrow R_2\overset{+}{N}{=}CH_2 + HOH$$

$$R_2NCH_2OH + H^+ \longrightarrow R_2NH_2^+ + CH_2O$$

Stewart and Bradley favor the formation of the iminium ion because of the stability conferred by the quaternization of the nitrogen.

Summary

1. The preparation of eight new 4-morpholinomethyl alkyl (or aralkyl) ethers has been described.

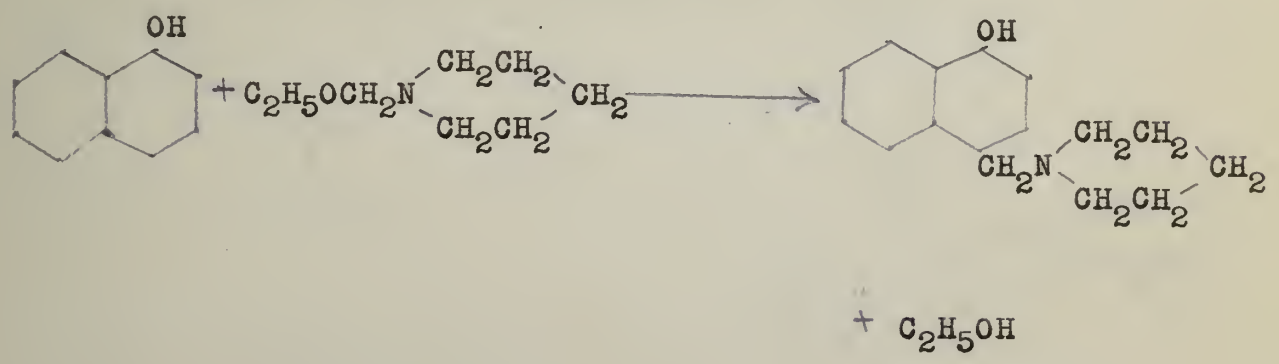
2. The amount of dimorpholinomethane formed by a competing reaction has been indicated in each preparation.

3. The variation of yield of the ethers with primary, secondary, and tertiary alcohols has been tabulated.

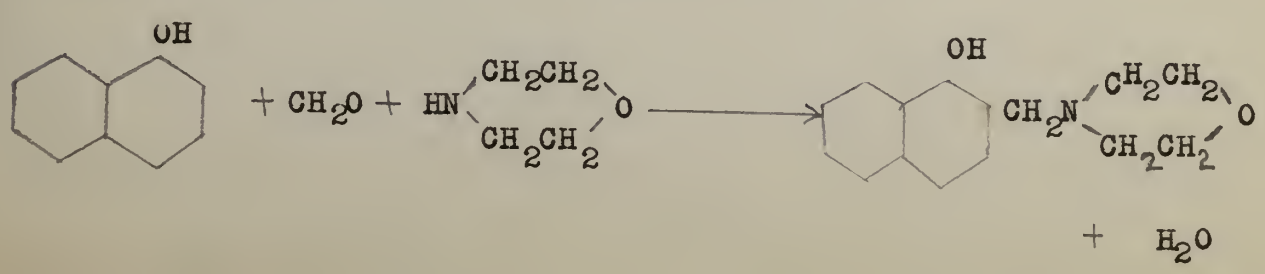
4. The introduction of binary and ternary mixtures for drying purposes has proved successful.

B. REACTIONS OF 4-MORPHOLINOMETHYL ALKYL ETHERS.

McLeod and Robinson (42) condensed diethylaminomethyl ethers with a wide range of compounds containing an activated methyl or methylene group. In most cases (ethyl cyanoacetate, resorcinol) the products were mixtures from which nothing could be isolated. Definite results were reported with acetophenone and 2,4-dinitrotoluene. Recently Tseou and Yang (52) have condensed piperidinomethyl ethyl ether with naphthols, cresols, and naphthylamines. With α-naphthol the following reaction occurred.

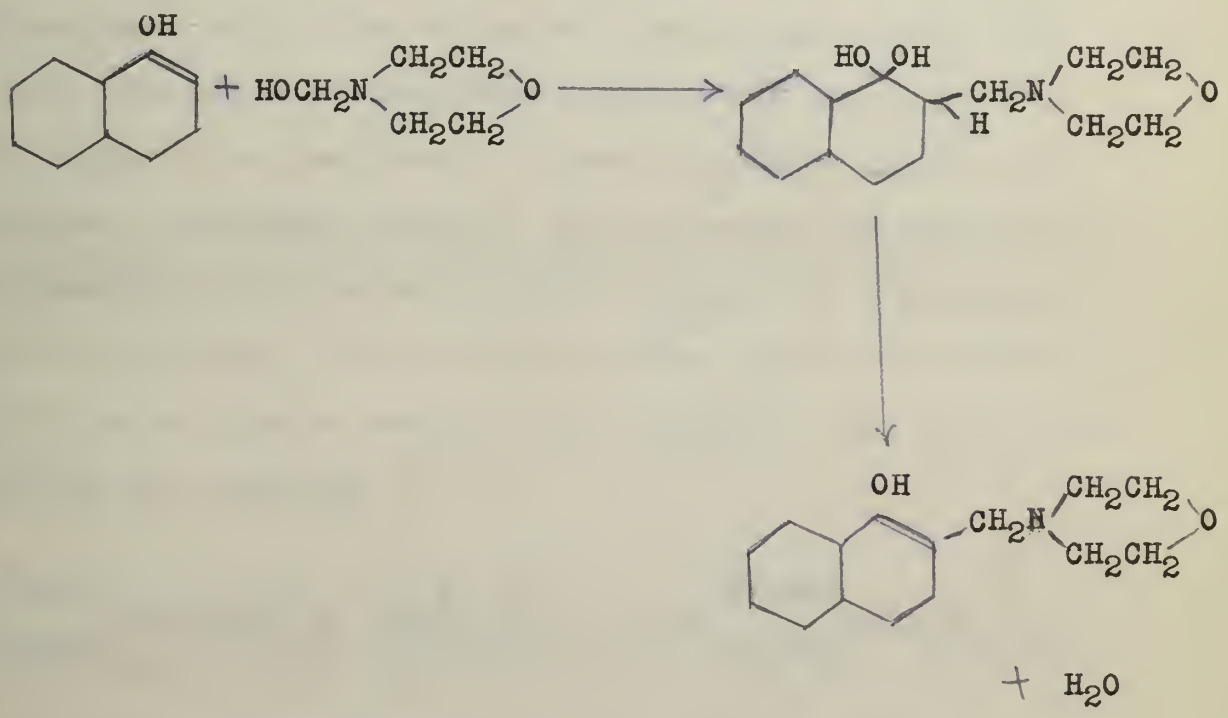


This reaction serves to introduce a dialkylaminomethyl group in the paraposition. The comparison with Caldwell's work (8) is interesting. Caldwell reinvestigated some of the morpholinomethyl phenols described by Bruson (5). α-Naphthol was treated with formaldehyde and morpholine. The following reaction occurred.



The latter reaction is a very convenient method to introduce a dialkylaminomethyl group in the ortho position. The ortho position was proven to be correct for hydrogenation of the aminomethyl naphthol yielded 2-methyl naphthol-1.

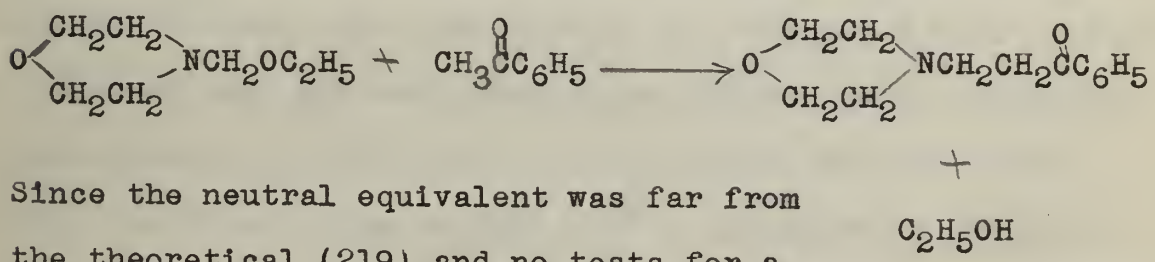
Caldwell compared the latter reaction with the formulation of the coupling of a diazo compound with naphthol-1.



The formation of an intermediate addition compound may account for ortho substitution. With the ether no intermediate compound is formed, thus para substitution occurs. Since the dialkylaminomethyl ethers are reactive, various reactions were carried out with 4-morpholinomethyl ethers.

1. 4-Morpholinomethyl ethyl ether and Acetophenone

In a 200 cc. round-bottomed flask 12 grams of acetophenone (0.1 mole), 14.5 grams (0.1 mole) of 4-morpholinomethyl ethyl ether and 50 grams of absolute ethyl alcohol were refluxed for one hour. The excess alcohol was distilled off, the residue was mixed with 60 cc. of dilute hydrochloric acid, and the neutral substances were removed by extraction with ether. The hydrochloric acid layer was made strongly basic with solid sodium hydroxide. The alkaline solution was then extracted with three 40 cc. portions of ether. The ether layers were combined, dried over Drierite, and the ether was removed on a steam-bath. At 6 mm. at 110-112°, 5 grams of a colorless oil was collected. The oil had a neutral equivalent of 93.4 and formed a picrate readily (M.P. 148-149°). The following reaction was expected.



Since the neutral equivalent was far from the theoretical (219) and no tests for a ketone were obtained, it was condluded that the oil was not β-morpholino propiophenone. The unexpected product was the dimorpholinomethane formed by the hydrolysis of the ether. The yield of dimorpholinomethane was 53.7 percent.

The procedure described above was that utilized by McLeod and Robinson (42) in the reaction of diethylamino-methyl iso-butyl ether with acetophenone. McLeod, after the

removal of the ethyl ether, obtained an oil which could not be crystallized. The oil was not distilled, purified, or analyzed. The oil formed a platinichloride and a picrate melting at 164° with decomposition. McLeod concluded that "there is little doubt that the product of the condensation is β-diethylaminopropiophenone." It is possible, however, that the product may have been tetraethylmethylene diamine. It is unfortunate that no neutral equivalent or analyses of the oil were reported. The work of McLeod was thus repeated.

Preparation of diethylaminomethyl iso-butyl ether:

In a 500 cc. round-bottomed flask 37 grams (0.5 mole) of iso-butyl alcohol was mixed with 37 grams (0.5 mole) of diethylamine. Fifteen grams of paraformaldehyde was added. The mixture, which became warm on shaking, was refluxed for thirty minutes. Then the mixture was saturated with potassium carbonate and put away over-night. Thepotassium carbonate was removed by filtration and the liquid was distilled. The fraction boiling at 130-165° at atmospheric pressure was collected and treated with sodium. Upon refractionation, the portion boiling at 163-164° (764 mm.) was collected.

Neutral equivalent:

Theoretical	154
Found	159

Reaction between the ether and acetophenone:

Acetophenone (12 grams) and the ether (16 grams) were mixed with 50 cc. of iso-butyl alcohol and refluxed for one

hour. After distilling away the excess iso-butyl alcohol, the residue was dissolved as far as possible in 2N HCl (50 cc.) andthe neutral substances were removed by ether extraction. The acid solution was separated and made alkaline with 50 percent sodium hydroxide solution. The precipitated oily layer was extracted with ether. The combined ethereal extracts were dried over solid sodium hydroxide. After the ether was removed, 3 grams of a colorless oil boiling at 63-65° (19 mm.) was collected. The neutral equivalent was found to be 89. At 762 mm., the oil distilled at 164-165°. Stewart and Bradley (51) prepared tetraethylmethylene diamine which boiled at 166-167°.

Neutral equivalent	
Found	89.0
Expected product	205.0
Tetraethylmethylene diamine	79.0

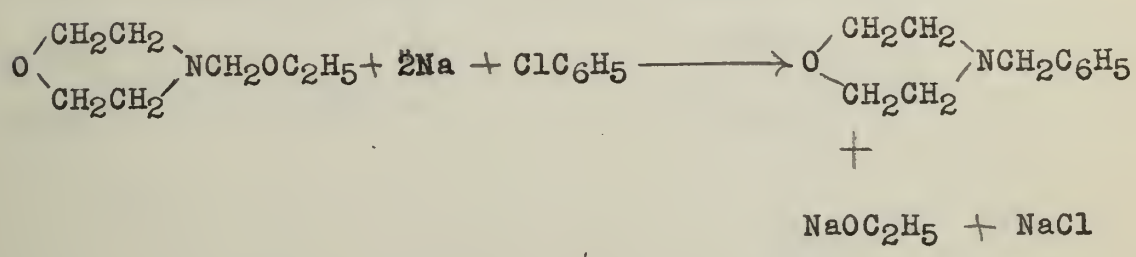
The neutral equivalent and boiling point of the product indicate that tetraethylmethylene diamine was actually formed. Theyield was 38 percent.

2. 4-Morpholinomethyl ethyl ether and Ethyl acetate.

In a 200 cc. round-bottomed flask were added 50 cc. of absolute ethyl alcohol, 9 grams (0.1 mole) of ethyl acetate, and 14.5 grams (0.1 mole) of 4-morpholinomethyl ethyl ether. The mixture was refluxed for one hour. The excess alcohol was removed and the residue was dissolved as far as possible in 75 cc. of dilute hydrochloric acid. The acid solution was extracted with three 20 cc. portions of ether to remove neutral substances and then made alkaline with sodium hydroxide. The alkaline solution was extracted with ether, the ether layers combined, and dried with Drierite. After the removal of the ether, 5.1 grams of a colorless oil distilling at 110-112° (6 mm.) was collected. The oil had a neutral equivalent of 93.3. Dimorpholinomethane was formed as in the preceding experiment. From this and the preceding experiment it was concluded that 4-morpholinomethyl ethyl ether does not react with acetophenone or ethyl acetate.

3. 4-Morpholinomethyl ethyl ether, Sodium, and Chlorobenzene.

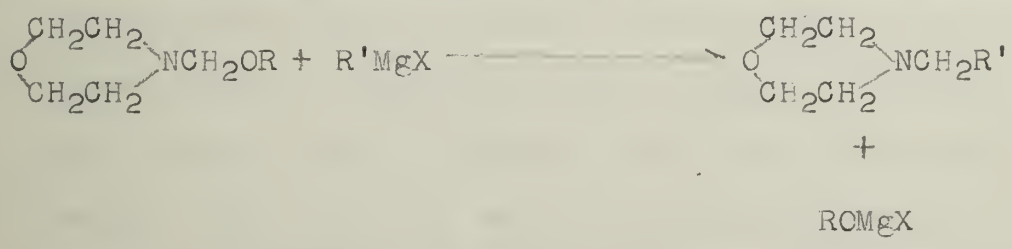
The preparation of benzyl morpholine by a modified Morton reaction (43) according to the following reaction was next attempted.



To 100 cc. of benzene were added 14.5 grams (0.1 mole) of 4-morpholinomethyl ethyl ether, 22.5 grams (0.2 mole) of chlorobenzene, and 4.6 grams (0.2 mole) of sodium. In thirty minutes the solution became reddish andthe flask became warm. At the end of 48 hours the sodium seemed to be entirely gone. A little ethyl alcohol added to react with unused sodium caused very little reaction. The mixture was then diluted with water and shaken until all the salt went into solution. After the two layers were separated, the water layer was made strongly alkaline with sodium hydroxide and extracted with ether three times. The ether solutions were added to the benzene solution and the mixture was dried over Drierite. Ether, alcohol, and benzene were removed on a steam-bath. At 15 mm. one gram of a colorless oil distilling at 134-136° was collected. The boiling point agrees with the boiling point of benzylmorpholine found in Table IV. The yield (6 percent) of product was surprisingly small.

4. 4-Morpholinomethyl ethers and Grignard reagents.

Robinson and Robinson (46) described the reaction of dialkylaminomethyl alkyl ethers and Grignard reagents as a convenient method of preparing tertiary amines. Table IV (Page 40) lists the N-substituted morpholines prepared according to the following reaction.



Experimental

Preparation of materials:

Tertiary butyl chloride: In a 500 cc. separatory funnel was placed 74 grams (1 mole) of tertiary butyl alcohol and 247 cc. (3 moles) of c.p. concentrated acid hydrochloric. After shaking for twenty minutes, the layers were separated. The upper layer was drawn off and washed with a 5 percent sodium bicarbonate solution, then with water until neutral to moist litmus paper. The chloride was dried over calcium chloride and distilled. The fraction boiling at 49.5-52° was collected (45).

Ether distilled over sodium, obtained from the J. T. Baker Chemical Company, was used throughout for all Grignard reactions. Before use this ether was treated with sodium and distilled. Magnesium turnings were kept

in a desiccator for one week before use.

Experiment #1:

The procedure developed by Robinson was first followed. The Grignard reagent was prepared from 1.6 grams (0.067 moles) of magnesium in a 500 cc. three-necked flask to which 10.51 grams (0.067 mole) of bromobenzene dissolved in 100 cc. of dry ether was added. After addition the mixture was refluxed for thirty minutes and cooled. Then 9.7 grams (0.067 mole) of 4-morpholinomethyl ethyl ether in 30 cc. of dry ether was added very slowly. A vigorous reaction persisted throughout. The mixture was refluxed on a steam-bath for thirty minutes and cooled. Water (100 cc.) was added slowly. After stirring and standing for thirty minutes, the layers were separated. The ethereal solution was extracted with four successive portions (50 cc. each) of dilute hydrochloric acid and the combined acid extracts were concentrated. The crystalline residue of benzylmorpholine hydrochloride was mixed with 100 cc. of 50 percent sodium hydroxide solution and 200 cc. of ether. The ether layer was taken off and dried over sodium hydroxide pellets. The ether was removed on a steam-bath. A dark-brown liquid remained which upon distillation yielded 2.5 grams of a colorless oil distilling at 112-115° at 8 mm. The yield of benzylmorpholine was 21.2 percent.

Neutral equivalent:	Theoretical	177
	Found	175

Experiment #2:

The concentration of the hydrochloric acid appeared tedious and unnecessary in the previous experiment. In this experiment the volumes of solutions were kept small and the concentration step was eliminated.

The Grignard reagent was prepared from 1.44 grams (0.06 mole) of magnesium and 7.59 grams(0.06 mole) of benzyl chloride in 100 cc. of dry ether. The mixture was refluxed one-half hour after addition and cooled. Seven grams (0.054 mole) of 4-morpholinomethyl methyl ether in 50 cc. of ether was added slowly. Again the mixture was refluxed one-half hour and cooled. Water was added to decompose the magnesium compound dissolved in the ether. After the layers were separated, the ether layer was extracted three times with 40 cc. portions of dilute hydrochloric acid. The extracts were combined and made alkaline with solid sodium hydroxide. The alkaline solution was then extracted with four 50 cc. portions of ether. The ethereal extracts were combined and dried over sodium hydroxide. After the ether was removed, 3.4 grams of a colorless oil distilling at 133-136° at 8 mm. was collected. The yield of phenethyl morpholine was 32.8 percent.

Neutral equivalent:	Theoretical	191
	Found	190

Experiment #3:

Acid hydrolysis was tried in place of hydrolysis by water alone. The Grignard reagent was prepared from 2.9

grams (0.12 mole) of magnesium and 15.2 grams (0.12 mole) of benzyl chloride in 100 cc. of ether. One-tenth mole of 4-morpholinomethyl ethyl ether (14.5 grams) in 50 cc. of ether was added. After refluxing, the mixture was then hydrolyzed by 100 cc. of water containing 10 cc. of concentrated sulfuric acid. The ether layer was extracted with three 20 cc. portions of 20 percent sulfuric acid. The acid extracts were combined and made alkaline with solid sodium carbonate. The alkaline solution was extracted with ether. The experiment was halted at this point since a precipitate of magnesium carbonate prevented an efficient extraction.

Experiment #4:

Solid sodium hydroxide was substituted for sodium carbonate in the neutralization of the acid extract. A heavy precipitate of magnesium hydroxide eliminated this method from further consideration.

Experiment #5:

The following procedure proved to be successful. Ammonium hydroxide andammonium chloride were used in the neutralization process to keep the magnesium salts in solution. The reaction mixture was left over-night before hydrolysis.

The Grignard reagent was prepared by the usual manner, using 2.9 grams (0,12 mole) of magnesium and 15.2 grams (0.12 mole) of benzyl chloride in 100 cc. of dry ether. One-tenth mole (14.5 grams) of 4-morpholinomethyl ethyl ether dissolved in 50 cc. of absolute ether was then, by a separatory funnel,

added slowly to the solution of the Grignard reagent, the mixture refluxed for thirty minutes and allowed to stand over-night. The mixture was hydrolyzed with 10 cc. of concentrated sulfuric acid dissolved in 100 cc. of water. The ether layer was extracted with three 20 cc. portions of 20 percent sulfuric acid. Ten grams of solid ammonium chloride was added to the combined acid mixture to which concentrated ammonium hydroxide (about 65 cc.) was added until the solution was alkaline. The alkaline solution was extracted with four 40 cc. portions of ether. The combined ether extracts were dried over calcium sulfate, the ether distilled, and the remaining oil was then distilled under reduced pressure. At 147-151° at 13 mm., 12.6 grams of a colorless oil was collected. The yield of phenethyl morpholine was 66 percent. This method was used for all the results reported in Table IV.

Neopentyl morpholine was prepared from tertiary butyl magnesium chloride and 4-morpholinomethyl ethyl ether. At 12 mm., 1.5 grams of a colorless oil distilling at 63-67° was collected. The yield of neopentyl morpholine was 10,0 percent.

Neutral Equivalent: (Neopentyl morpholine)	Theoretical	157
	Found	150

The experiment was repeated three times but the yield was not increased and the product gave no better neutral equivalent. The Grignard reaction always proceeded smoothly,

indicating that the tertiary butyl chloride was dry. No explanation of the small yield was found. When other 4-morpholinomethyl ethers were used, the results were the same. It is of interest to note that 4-morpholinoethyl ethers do not undergo any reaction with Grignard reagents (37).

TABLE IV

N-Morpholine	B.p. °C.	B.p. Mm.	Yld. %	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate M.P. °C. (Cor.)	Nitrogen, % Calcd.	Nitrogen, % Found
β-Phenethyl	147-151	13	66	191	190	7.33	7.31	166-167	13.33	13.27
α-Naphthylmethyl	185-190	9	57.7	227	225	6.17	6.00	209-211	12.28	12.40
n-Propyl	43-46	7	43.4	129	130.3	10.85	10.76	118-120	15.64	15.67
n-Hexyl	86-87	6	59.7	171	172	8.18	8.04	110-111	13.99	13.97
Benzyl	135-136.5	14	64.4	177	176.8	7.91	7.35	193.5-195	13.79	13.65
* Neopentyl	63-67	12	10.0	157	150					

* No Analysis since compound could not be purified.

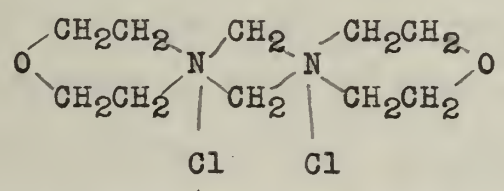
Summary

1. Six alkyl (or aralkyl) morpholines have been prepared from 4-morpholinomethyl ethers and Grignard reagents.

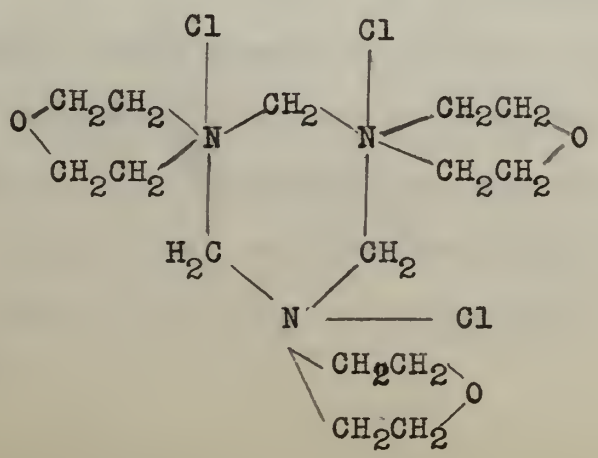
2. The ammonium chloride and ammonium hydroxide method of holding the magnesium salts in solution proved successful in the isolation of substituted morpholines from acid solutions containing magnesium.

II. ATTEMPTED PREPARATION OF 4-MORPHOLINOMETHYL CHLORIDE.

Mason and Block (39) described the preparation and polymerization of β-4-morpholino-ethyl chloride. Due to the greater reactivity of 4-morpholinomethyl derivatives it was expected that 4-morpholinomethyl chloride would be difficult to isolate. Polymerization was expected to occur much more readily. If polymerization is analogous to that of 4-morpholinoethyl chloride, the following polymer would be formed.



This compound should be less stable than the 4-morpholino-ethyl chloride polymer since the middle ring is a four-membered ring. The middle ring may be considered to be a cyclobutane ring for nitrogen is tetrahedral and can be substituted for carbon in many ring systems (19). The following compound, which would be more stable, was held a more likely possibility.



Experiment #1:

To 50 cc. of chloroform was added 7.5 grams (0.25 mole) of paraformaldehyde and 22 grams (0.25 mole) of morpholine. Thionyl chloride (35.7 grams) was added very slowly. A vigorous reaction occurred. After all the thionyl chloride was added (one hour), the reaction mixture was refluxed for one hour. Sulfur dioxide was given off and the mixture became progressively darker. The mixture was allowed to stand over-night and filtered. Eight grams of an impure solid was collected. Two recrystallizations from alcohol and ether yielded a white crystalline solid melting at 174-176°. The melting point of morpholine hydrochloride is 176°. A mixture of the product and morpholine hydrochloride melted at 174°. Morpholine hydrochloride was the only product isolated.

Experiment #2:

In order to prevent the formation of morpholine hydrochloride during the reaction, morpholine hydrochloride was used as one of the starting materials. To 50 cc. of chloroform was added 12.4 grams (0.1 mole) of morpholine hydrochloride and 6 grams (0.2 mole) of paraformaldehyde. The thionyl chloride (23.8 grams) was added slowly. After the addition was complete, the mixture was refluxed for one hour and cooled. A white precipitate came down. The solid was filtered off, dried, and recrystallized twice from alcohol and water. The solid was identified as morpholine hydrochloride.

Experiment #3:

The procedure was the same as that in the previous experiment but the addition of thionyl chloride was carried out at the boiling point of chloroform. Morpholine hydrochloride was obtained in this experiment also.

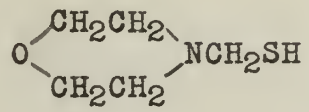
Experiment #4:

To 50 cc. of chloroform was added 6.2 grams (0.05 mole) of morpholine hydrochloride and 3 grams (0.1 mole) of para-formaldehyde. Dry hydrogen chloride was then passed into the mixture for one hour. Ether was added to the chloroform to precipitate a white solid. The solid, when recrystallized from alcohol and ether, melted at 173-176°. The solid was added to 50 percent sodium hydroxide solution and the alkaline solution was extracted three times with ether. The ether extracts were combined and dried over Drierite. After the ether was driven off, a liquid boiling at 124-126° was obtained. The oil was identified as morpholine, showing the original solid to be morpholine hydrochloride.

At thispoint the problem was dropped since nothing but morpholine hydrochloride could be isolated. Houben and Arnold (32) allowed diethylamine to react with chloromethyl sulphate (31). The product, diethylaminomethyl chloride, was found to be very unstable and was isolated in a very small yield only as chloroplatinate.

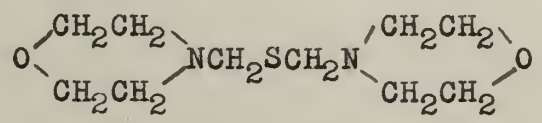
It is interesting to note that morpholine, formaldehyde, and hydrogen sulfide form 4-morpholinomethanethiol which is a solid melting at 86-89°.(3)

4-Morpholinemethanethiol

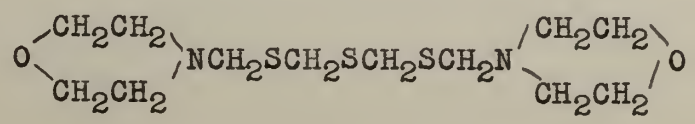


(3)

4-Morpholinemethanol is unstable. The substitution of oxygen by sulfur confers stability to the compound. While piperidine, formaldehyde, and hydrogen sulfide condensed to form 1-piperidinomethanethiol, the presence of hydrochloric acid was required for the formation of the 4-morpholinemethanethiol. This is odd because the addition compounds of amines and aldehydes are sensitive to acids. It appears unusual that two secondary amines of such apparent similar nature should act so differently. Corresponding to results obtained with piperidine, morpholine yielded 1,3-di(4'-morpholine)-2-thiapropane.



Morpholine, however, yielded an additional compound which had no analogue in the piperidine reaction. Two molecules of the 4-morpholinemethanethiol reacted with one mole of di-(hydroxymethyl) sulfide to yield 1,7-di-(4'-morpholine)-, 2,4,6-trithiaheptane.



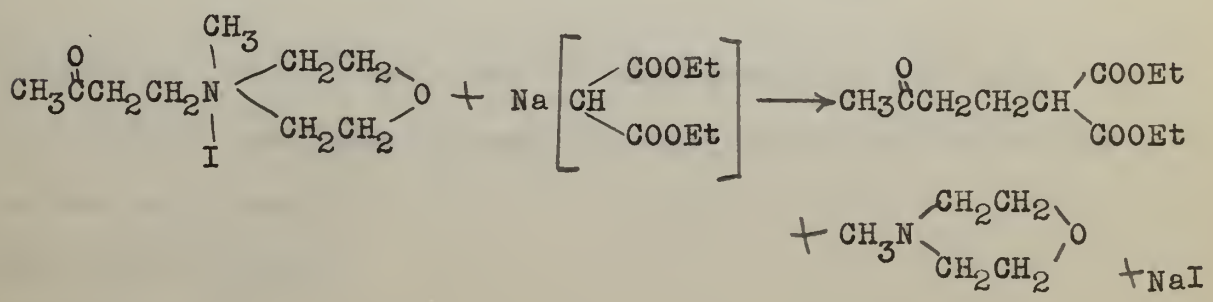
One, therefore, must not conclude that if a reaction proceeds with piperidine, the similar compounds will be formed with

morpholine because both are secondary amines.

III. MORPHOLINE, FORMALDEHYDE AND KETONES.

According to Whitmore (53), secondary amines and formaldehyde form R_2NCH_2OH which can react with acetone so that from one to six hydrogen atoms are replaced by the $-CH_2NR_2$ group. Theoretically all the alpha hydrogen atoms of any ketone should be replaced by $-CH_2NR_2$ groups. The problem of preparing morpholinoketones seemed interesting for reduction of amino ketones yields amino alcohols, the esters of which are good anaesthetics (4). The problem was discarded when a literature search indicated that Harradence and Lions (24) reported the preparation of a number of morpholino ketones.

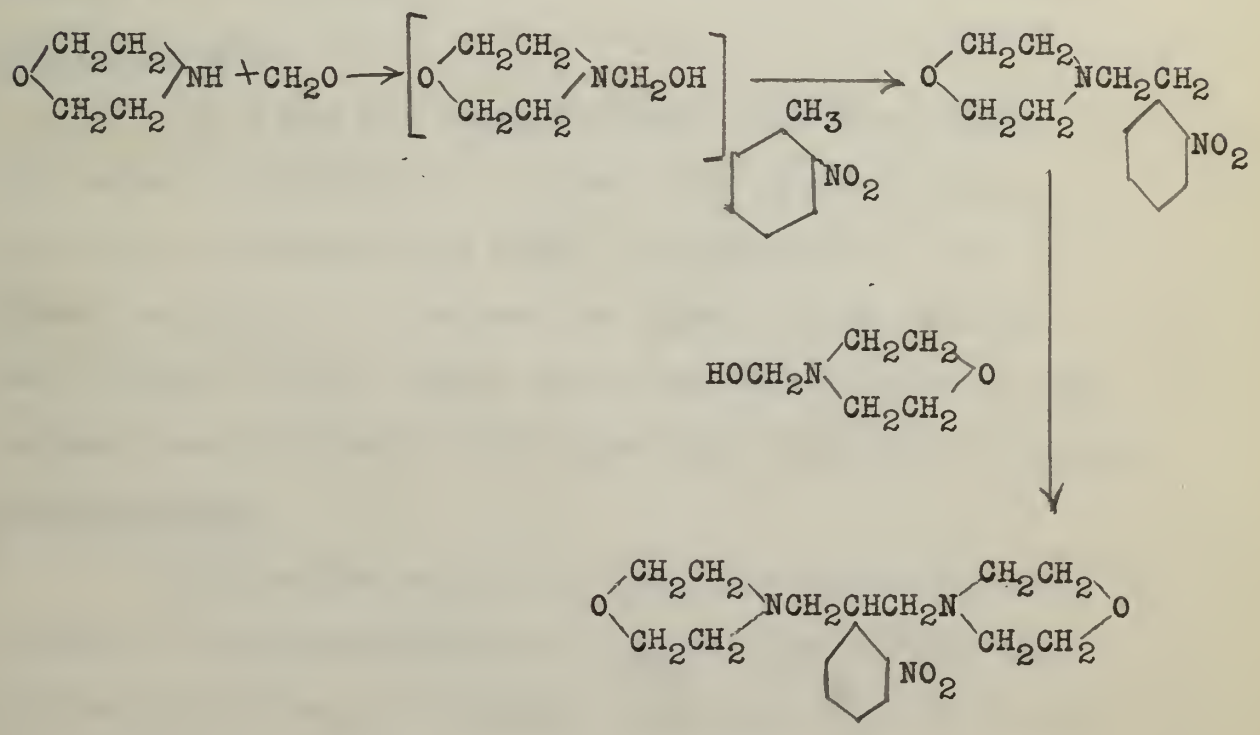
Harradence (24) condensed ketones containing reactive methylene groups with paraformaldehyde and morpholine hydrochloride. Acetone, cyclohexanone, and cyclopentanone were among the ketones used. The amino ketones were reduced to amino alcohols and the esters were made. The most powerful anaesthetic found was the hydrochloride of the benzoate of 1-morpholinobutanol-3. The following reaction of the methyl iodide derivatives deserves mention.



IV. MORPHOLINE, FORMALDEHYDE AND NITROTOLUENES.

Gilman (22) implies that ortho and para nitrotoluenes undergo the same reactions that nitromethane undergoes because of the principle of vinylogy. Since the hydrogen atoms in nitromethane are active, the following reaction may be formulated for o-nitrotoluene, formaldehyde and morpholine.

I.



II.

Compounds I and II are theoretically possible. In order to activate the methyl groups 2,4-dinitrotoluene was tried in one experiment.

Ortho Nitrotoluene

Experiment #1:

In a 500 cc. flask 17 cc. (0.2 mole) of formalin and 17 cc. (0.2 mole) of morpholine were mixed together with cooling. One-tenth mole (13.7 grams) of o-nitrotoluene was added and the mixture was allowed to stand over-night. Two layers appeared. Upon distillation of the lower layer, 11 grams of a yellow oil boiling at 106-108° at 15 mm. was collected. Pure o-nitrotoluene distilled at 106-107° at 15 mm. Only unreacted o-nitrotoluene was collected.

Experiment #2:

In a 200 cc. round-bottomed flask were mixed 17.4 grams of morpholine, 6 grams of paraformaldehyde, and 15 cc. of benzene was added. o-Nitrotoluene (13.7 grams) in 15.0 cc. of benzene was added and the mixture was refluxed for two hours. After the distillation of the benzene, most of the o-nitrotoluene was collected unchanged.

p-Nitrotoluene

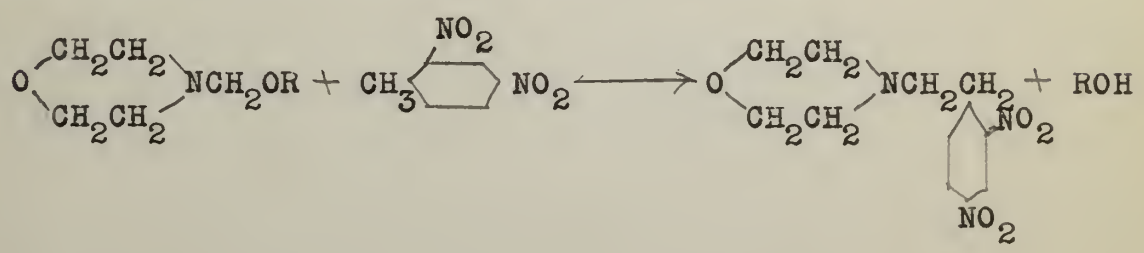
Two-tenths mole (17.4 grams) of morpholine and 6 grams of paraformaldehyde were mixed with cooling and diluted with 15 cc . of benzene. One-tenth mole (13.7 g.) of p-nitrotoluene in 15 cc. of benzene was added and the mixture was refluxed for three hours. After the benzene was distilled off, a yellow oil boiling at 138-139° at 27 mm. was collected. Over-night the oil solidified in an ice-bath. The solid melted at 48.5-49°. Thus only the original starting material was collected.

2,4-Dinitrotoluene

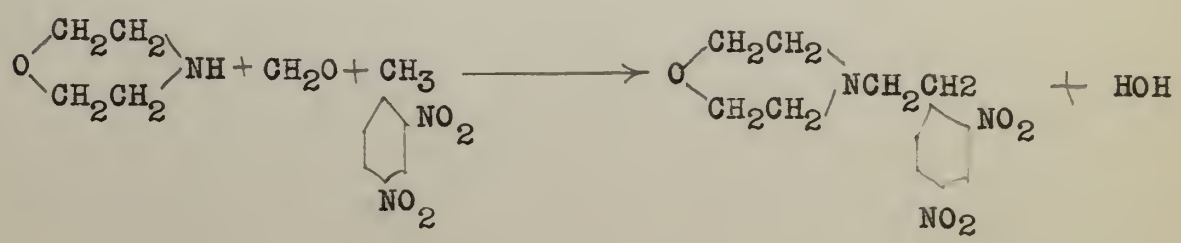
4-Morpholinemethanol was prepared according to Binz and Pence (3). To 17 cc. of formalin, 17 cc. of morpholine was added with cooling. Ten grams of potassium carbonate was added and the mixture was then allowed to stand for one hour. The upper layer of 4-morpholinemethanol was separated. A mixture of 18.2 grams (0.1 mole) of 2,4-dinitrotoluene and 20 cc. of benzene was added and the reaction mixture was refluxed for three hours. After the benzene was removed the product was distilled at reduced pressure. Upon distillation, the product decomposed and an explosion occurred.

Condensations with nitrotoluenes were terminated at this point. No evidence of a reaction was indicated in any experiment. In each of the following reactions, the same product theoretically should be formed.

a)



b)

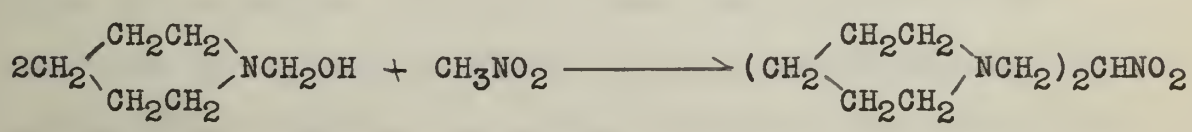


The second reaction is simpler since the formation of the

4-morpholinomethyl ether is eliminated. McLeod (42) has described a reaction involving diethylaminomethyl iso-amyl ether and 2,4-dinitrotoluene but the product was not distilled or analyzed.

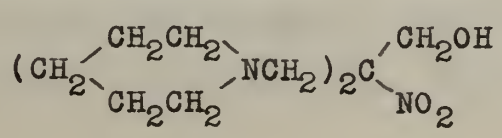
V. MORPHOLINE, FORMALDEHYDE AND ALIPHATIC NITRO COMPOUNDS.

In 1905 Henry (26) investigated the reaction of nitro compounds with piperidinomethyl alcohol. He found that methyl alcohol did not react with nitromethane, but the introduction of the NR_2 group in methyl alcohol then produced the following reaction:



At first Henry thought that three piperidinomethyl groups were introduced because nitroparaffins can combine with as many formaldehyde groups as free hydrogen atoms adjacent to the NO_2 group.

Actually Henry found that only two hydrogen atoms are replaceable by piperidinomethyl groups. The di-piperidinomethyl nitromethane when mixed with formaldehyde yielded



Since the compound was prepared from tri-hydroxymethyl nitromethane and piperidine or from piperidinomethanol and nitroethyl alcohol, Henry concluded that di-piperidino-methyl hydroxymethyl nitromethane represented a stability maximum. The introduction of a third dialkylaminomethyl group produced an unstable compound. Later Duden, Bock, and Reid (12) showed that two hydrogen atoms of nitromethane can be replaced by dialkylaminomethyl groups. With piperidine, formaldehyde, and nitroethane Henry reported the isolation of 1,3-dipiperidino-2-nitro-2-methylpropane. The two hydrogen atoms on the carbon attached to nitrogen were replaced by dialkylaminomethyl groups.

In 1937 Cerf de Mauny (9) reported the reaction of secondary amines, formaldehyde, and aliphatic nitro compounds. He concluded that the vigor of the reaction is diminished as the molecular weight of the nitro compound increases. The following rule was postulated:

"If, in the molecule of an aliphatic nitro compound, the carbon atom to which the nitro group is attached is linked to n atoms of hydrogen, the number of molecules of methylolamine that it is capable of fixing is n-1."

The condensation did not work with secondary aromatic amines, primary amines (ammonia and its derivatives), secondary nitro compounds, and compounds containing a nitro group that is attached to a carbon having a double bond. When formaldehyde

was replaced by higher aldehydes, the condensation also failed to work. No experiments with morpholine were described.

Cerf de Mauny does not agree with Henry who reported the replacement of two hydrogen atoms in nitroethane. According to Cerf de Mauny's rule only one hydrogen in nitroethane should be replaced. The rule was postulated on the results of experiments with nitromethane, 1-nitropropane, and 1-nitrooctane. No evidence of experiments with nitroethane are reported in the paper.

Experiments with morpholine, formaldehyde, and nitromethane, nitroethane, and 1-nitropropane were undertaken to determine the number of hydrogen atoms substituted in each case. Since the preliminary experiments were performed with 1-nitropropane, the work with 1-nitropropane will be described first.

1-Nitropropane

Experiment #1:

Morpholine (17 cc.) was added gradually with cooling to 18 cc. of 37 percent formalin. There was added to the reaction mixture 10 grams of anhydrous potassium carbonate with vigorous shaking to give an upper layer of 4-morpholinemethanol (3) which was separated and dried over potassium carbonate. The 4-morpholinemethanol was mixed with 50 cc. of benzene in a 200 cc. round-bottomed flask. Two-tenths

of a mole (17.8 grams) of 1-nitropropane was added and the mixture was refluxed for one hour. The benzene was then removed on a steam-bath. Decomposition of the product resulted upon distillation at reduced pressures.

Experiment #2:

When paraformaldehyde was substituted for formalin, decomposition of the product also occurred.

Experiment #3:

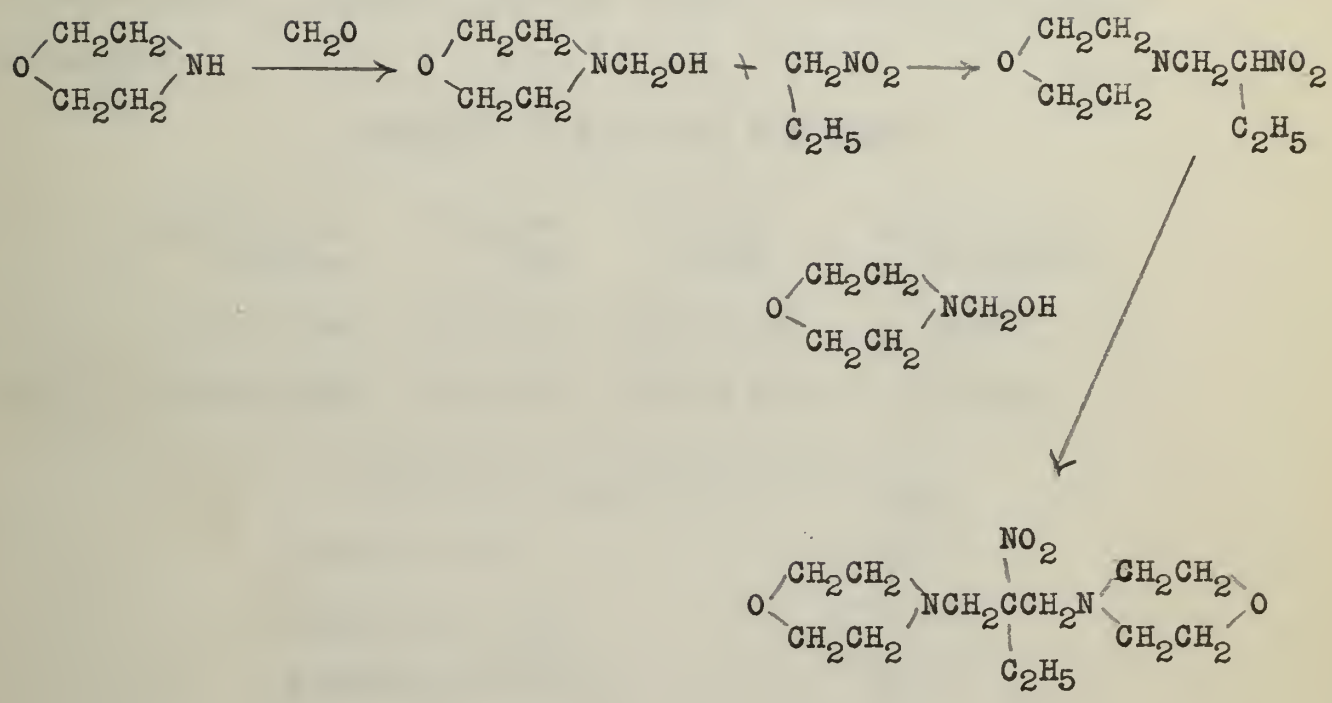
The following procedure, that of Cerf de Mauny, was used in all succeeding experiments. To 17 cc. of 37 per cent formalin was added 17 cc. of morpholine with cooling. Two-tenths of a mole (17.8 grams) of 1-nitropropane was added at 0°. The mixture was shaken and allowed to stand for two days. Two layers separated. The lower layer, which was water-soluble, was discarded. The upper layer was fractionated with an efficient column. At 15 mm., 25.6 grams of a colorless oil boiling at 134-136° was collected.

Analysis of the oil: Kjeldahl.

	Weight of Sample	0.0981N HCl	0.1188N NaOH	Percent of Nitrogen
I	0.2745 gms.	48.00 cc.	15.41 cc.	14.68
II	0.2370 gms.	48.00 cc.	18.73 cc.	14.69

There are two theoretically possible reactions, as follows:

I.



II.

Theoretical percent of nitrogen

I	14.89
II	14.64

The values are so close that no conclusion can be obtained from a nitrogen analysis. According to the rule previously stated, compound I is the expected product. Since Cerf de

Mauny (9) reported that secondary nitro compounds do not condense with formaldehyde and secondary aliphatic amines, compound I would not be expected to react further to form compound II. On the assumption that the product is I, the yield was 68.1 percent. The oil formed a picrate melting at 120-122°.

Analysis of picrate: Kjeldahl.

	Weight of Sample	0.1000N HCl	0.1003N NaOH	Percent of Nitrogen
I	0.2579 gms.	49.00 cc.	18.51 cc.	16.53
II	0.2640 gms.	49.00 cc.	17.68 cc.	16.59

Theoretical percent of nitrogen

Picrate of I	16.79
Dipicrate of II	16.91
Monopicrate of II	16.21

While the percentages here are very close also, the analysis of the picrate tends to substantiate the formation of compound I.

Equivalent weight: Samples of the oil (0.3 grams) were dissolved in 10 cc. of 95 percent ethyl alcohol and titrated with .1N hydrochloric acid to a methyl orange end-point. The end-points were not very sharp and were difficult to determine. Values of 195 and 201 were the best checks obtainable. The equivalent weight of compound I is 188; that of II, 287.

Reduction:

Experiment #1:

From piperidine, formaldehyde and 1-nitropropane, Cerf de Mauny (9) obtained 1-piperidino-2-nitrobutane which was reduced to the amine with zinc and gaseous hydrogen chloride in alcoholic medium. The same procedure was attempted for the morpholine analogue.

Eighteen grams of 1-morpholino-2-nitrobutane was dissolved in 50 cc. of absolute ethyl alcohol and 13 grams (0.2 mole) of zinc was added. Hydrogen chloride from a generator (sodium chloride and concentrated sulfuric acid) was passed in for four hours. The mixture was filtered and the white solid was mixed with 100 cc. of 50 percent sodium hydroxide solution. The alkaline solution was extracted four times with 50 cc. portions of ether. The ether extracts were combined and dried over Drierite. After the ether was taken off, a few drops of an oily residue remained. This residue was discarded. Distillation of the original alcoholic filtrate also yielded no product.

Experiment #2:

One-tenth mole (18.8 grams) of 1-morpholino-2-nitrobutane was mixed with 30 grams of mossy tin in a 500 cc. three-necked flask equipped with a mercury-sealed mechanical stirrer and a reflux condenser. Concentrated hydrochloric acid (60 cc.) was added slowly. After the addition of the acid, the mixture was heated on a steam-bath for two hours. The mixture was then

made alkaline with stong (50%) sodium hydroxide solution. The sodium hydroxide was added until almost all of the tin salts went into solution. The alkaline solution was then extracted with four 60 cc. portions of ether. The ether layers were combined and dried over sodium hydroxide pellets. After the ether was removed, 2.8 grams of a colorless oil boiling at 85-87° at 4 mm. was collected.

Experiment #3:

Upon the addition of sodium hydroxide solution in the previous experiment, it was noticed that many times the tin salts did not all go into solution. Extraction of the product was thus difficult. To facilitate the separation, tin was separated from the acid solution as the sulfide before the alkali was added. (29).

The nitro compound (28 grams) was mixed with 30 grams of mossy tin. Concentrated hydrochloric acid was added (70 cc.) slowly. The mixture was heated on a steam-bath for two hours, diluted with 300 cc. of water, and saturated with hydrogen sulfide. The precipitate of tin sulfide was filtered off and the filtrate concentrated on a steam-plate. The solution was then made alkaline and worked up as described in experiment #2. At 14 mm., 14.1 grams of a colorless oil boiling at 102-104° was obtained. The yield of 1-morpholino-2-aminobutane was 60 percent.

Experiment #4:

Catalytic reduction with Raney nickel was next undertaken. Raney nickel was activated according to the method of Covert and Adkins (10).

Raney nickel,150 grams, was added slowly (2 hours) to a solution of 150 grams of sodium hydroxide in 600 cc. of water in a two-liter beaker surrounded by ice. The mixture was then heated on a steam-bath and then a hot-plate for four hours at 115-120°. A further 200 cc. of a 20 percent solution of sodium hydroxide was added and the mixture was kept at 115-120° for three hours. The mixture was washed after decantation until neutral to litmus paper. The nickel was kept under alcohol in a glass stoppered bottle.

A Parr Hydrogenation Apparatus of the low pressure type (2) was utilized to reduce the 1-morpholino-2-nitrobutane. The apparatus was tested for leaks and found to be satisfactory. In a bottle one-tenth mole (18.8 grams) of the nitro compound was dissolved in 160 cc. of 95 percent ethyl alcohol. Eight grams of activated Raney nickel was added and the bottle was connected to the Parr Hydrogenator. The bottle was evacuated and then filled with hydrogen under a pressure of 45 pounds. The bottle was shaken until the pressure gauge assumed a constant reading. It was noticed that at the beginning an interval of two minutes elapsed before hydrogen was absorbed.

	Start	End
Time	10:15	11:15

Pressure	45 lbs.	21 lbs.
Temperature	30.5°	30.6°

The bottle was shaken for three hours more but the reading at 2:15 was exactly the same. The solution was filtered and the alcohol was distilled off. At 14 mm., 8 grams of a colorless oil boiling at 102-104° was collected. Theproduct was obviously identical with the oil isolated from the reduction with tin and acid. The yield of 1-morpholino-2-aminobutane was 50.6 percent.

Analysis of the reduction product: Kjeldahl.

	Weight of Sample	0.1000N HCl	0.1101N NaOH	Percent of Nitrogen
I	0.3173 grams	50.00 cc.	10.60 cc.	16.91
II	0.3338 grams	50.00 cc.	8.83 cc.	16.89

Calculated for $C_8H_{18}N_2O$ - N = 17.72

The oil was redistilled twice andthe purified samples were analyzed. All analyses checked the above values.

Equivalent weight: Titrations with acid using methyl orange or bromophenol were completely unsatisfactory. The end-points were not sharp.

Molecular weight: Since the nitrogen analysis andthe equivalent weight of the reduced compound were not satisfactory, a determination of the molecular weight by depression of the freezing point was performed. The method was that described by Getman and Daniels (18). The molecular weight was then

calculated from the following formula.

$$\text{Molecular weight} = \frac{1000 \times \text{molal depression of solvent} \times \text{grams of solute}}{\text{grams of solvent} \times \text{observed lowering of freezing point}}$$

	Wt. of Solute	Wt. of Benzene	Molal depression of benzene	Lowering of freezing pt.
Expt. #1	0.1764g.	22.5666g.	5.12	0.25
Expt. #2	0.1845g.	22.4953g.	5.12	0.26

Substitution in the formula indicated the molecular weight of 160.9 and 161.4. The molecular weight of 1-morpholino-2-aminobutane is 158.

Derivatives of the reduced compound:

Acetyl derivative: To 5 cc. of acetic anhydride was added 1 cc. of the amine. The mixture was heated for five minutes and poured into 50 cc. of distilled water and allowed to stand for one-half hour. No precipitate formed.

p-Bromobenzenesulfonamide (38): To 0.01 mole (1.58 grams) of the amine was added 0.005 mole (1.28 grams) of p-bromobenzenesulfonyl chloride. Heat was given off andthe mixture rapidly turned orange. Within two minutes the entire mass was turned into a gum. The product was heated on a steam-bath for one-half hour and then put away in an ice-box. No precipitate appeared after standing for one week.

Benzoyl derivative (50): The Schotten-Baumann reaction with benzoyl chloride yielded a waxy solid. Recrystallization from ethyl alcohol and water yielded waxy crystals. The product was not analyzed.

Reduction with tin and hydrogenation with a catalyst are the standard methods for converting a nitro group to an amino group. It seemed unusual that the analyses and the derivatives did not conclusively indicate a primary amine. Fieser (16) recently described the first instance of the conversion of nitro compounds to hydroxylamines by hydrogenation. The formation of a hydroxylamine can not be reconciled with the molecular weight determination (molecular weight of the expected hydroxylamine is 174). The reduced product gave no test with Tollen's reagent.

Phenyl Isocyanate: To one gram of the reduced compound was added one cubic centimeter of phenyl isocyanate. The mixture became warm, reddish-colored, and soon turned into a thick gum.

α-Naphthyl Isocyanate: The above procedure also yielded a gum of no value as a derivative.

Hydrochloride: When dry hydrogen chloride was passed through a solution of the reduced compound in benzene, a gelatinous precipitate was formed. The derivative was very sticky, could not be dried, and was thus discarded. Evaporation of a mixture of the reduced compound in concentrated hydrochloric acid yielded the same sticky substance.

3,5-Dinitrobenzoate (7): One-hundredth mole (1.58 grams) of the reduced compound was dissolved in 25 cc. of absolute ethyl alcohol. One-hundredth mole (2.12 grams) of 3,5-dinitrobenzoic acid was also dissolved in 25 cc. of absolute ethyl alcohol. The solutions were poured together in a beaker and the mixture was allowed to evaporate. After standing for three days, the yellow solid was filtered off and dried. The yellow solid was recrystallized four times from absolute ethyl alcohol. The pure yellow crystals melted at 162-163°.

Analysis for nitrogen

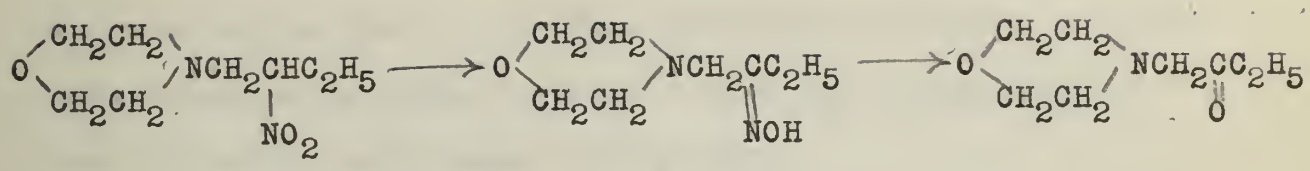
	Weight of Sample	0.09827N HCl	0.1011N NaOH	Percent of Nitrogen
I	0.1774 gms.	49.00	29.08 cc.	14.80
II	0.2314 gms.	49.00 cc.	23.42 cc.	14.81

Calculated for $C_{15}H_{22}N_4O_7$

N : 15.14

Reduction of 1-morpholino-2-nitrobutane to the oxime:

Johnson and Degering (33) partially reduced nitroparaffins to oximes. The oximes were hydrolyzed with acid and the ketones or aldehydes formed were distilled and identified with hydroxylamine hydrochloride. Following their procedure, an attempt was made to prepare 1-morpholino-butanone-2 which boils at 97-100° at 9 mm. (47).



To 110 cc. of glacial acetic acid and 11.5 grams of 1-morpholino-2-nitrobutane was added 35 grams of zinc dust. The mixture was stirred and refluxed for three hours, then refluxed for four hours. The oxime was hydrolyzed by adding 25 cc. of water and 8 cc. of concentrated sulfuric acid and heating on a steam bath for three hours. The solution was cooled and made alkaline with sodium hydroxide solution. The alkaline solution was extracted with ether and the ether was dried over solid sodium hydroxide. After the ether was taken off, only a few drops of liquid remained. No product could be isolated.

Johnson and Degering distilled the ketone from acid solution. With morpholine the products are not volatile and can not be separated simply by distillation from basic solution. It is interesting to note that Johnson reduced several nitroparaffins with iron and hydrochloric acid. The acid solution was made alkaline and the amine was distilled into standard acid. This method is of limited application, for nitro compounds whose reduction compounds are volatile and can be distilled from alkaline solution. With a morpholine residue part of a

nitro compound this method is not applicable. The reduced compound would have to be extracted with an organic solvent from alkaline solution. In such a case the precipitate of iron hydroxide would cause difficulty.

1-Morpholino-2-Nitrobutane, a solvent for cellulose acetate.

A good, cheap solvent for cellulose acetate would be commercially attractive. Morpholine and formaldehyde are cheap chemicals. Nitropropane should become fairly reasonable with the increase of vapor phase nitrations. Thus the raw materials for making 1-morpholino-2-nitrobutane can be considered cheap chemicals. The reaction forthe preparation of the nitro compound is simple, requires no special apparatus, and the yield of product is good.

Cellulose acetate (15) dissolves readily in 1-morpholino-2-nitrobutane. Various diluents were tried. Kerosene can not be used since it is not miscible with the morpholine derivative. Butyl alcohol is miscible but throws out the acetate upon dilution. Ethyl alcohol is of no value as a thinner, but acetone can be used in small quantities.

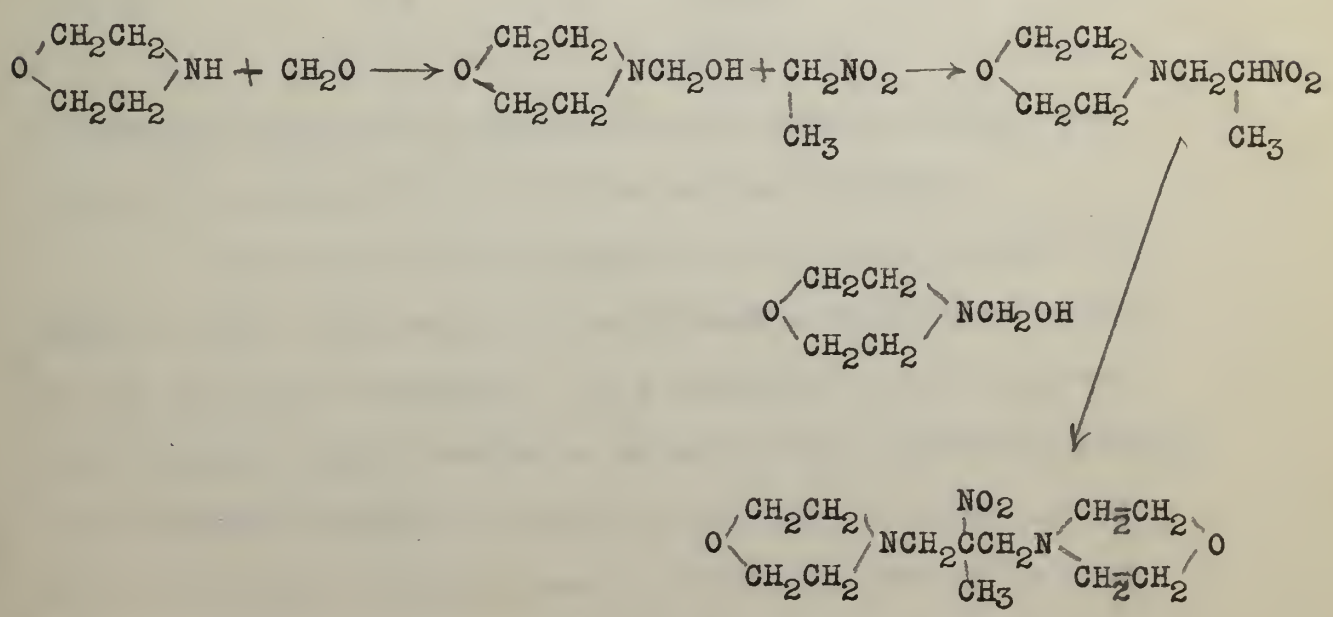
Nitromethane proved to be similar to 1-morpholino-2-nitrobutane as a solvent for cellulose acetate. The diluents described above worked exactly the same with nitromethane. It seemed hardly likely that a compound formed from formaldehyde, morpholine, and 1-nitropropane would ever be cheaper than nitromethane alone. Since the solvent power of the morpholine compound does not, as shown by the above diluents, offer

any special advantages over that of nitromethane, the problem was dropped. As a solvent useful in laboratory experiments, the morpholine compound is interesting, but its application in industry on a basis of price is limited.

Nitroethane:

To 17 cc. (0.2 mole) of 37 percent formaldehyde and 17 cc. (0.2 mole) of morpholine was added 7.50 grams (0.1 mole) of nitroethane. The mixture was shaken with vigor and allowed to stand over-night. On the next day a solid separated out. The solid was filtered off and recrystallized from absolute ethyl alcohol. Fine white needles melting at 124-125° were obtained. The weight of the crude product was 25 grams, that of the recrystallized material 19 grams. The following reactions are theoretically possible:

I.



II.

It is interesting to note that mere calculation of yield eliminates the formation of compound I. Based on the one-tenth mole of nitroethane used, one-tenth mole of I (17.4 grams) or one-tenth mole of II (27.3 grams) are theoretically possible. Since 19 grams of a pure product was obtained, an amount greater than the theoretical yield of I, the formation of I appears unlikely. On the assumption that the product is compound II, theyield was 69.6 percent. The product, unlike the 1-nitropropane product, formed morpholine picrate.

Analysis of the product: Kjeldahl.

	Weight of Sample	0.1000N HCl	0.1003N NaOH	Percent of Nitrogen
I	0.2514 gms.	50.00 cc.	23.00 cc.	15.00
II	0.2677 gms.	49.00 cc.	20.35 cc.	14.95

I	16.09
II	15.38

The neutral equivalent was not taken since the solid was found to be insoluble in all the common solvents.

Compound II was unexpected. According to Cerf de Mauny's rule, compound I is the product. Therule is based on the fact that compound I is a secondary nitro compound and secondary nitro compounds do not react with formaldehyde and secondary amines. In several experiments with secondary nitro compounds the replacement of hydrogen by an amino-methyl group was not attained. It may be possible that

when a secondary nitro compound is formed in a reaction, its reactivity is much different from a stock sample of the same compound. A "nascent" secondary amine may undergo the condensation.

In the experimental procedure it will be noticed that two moles of morpholine and formaldehyde were used for one mole of nitroethane. The experiment was repeated with a mole for mole ratio but the same product was isolated. Theyield of solid in the first experiment was much greater. The ratio of morpholine and formaldehyde compared to 1-nitropropane was also increased in the expectation of having two hydrogen atoms replaced by a morpholinomethyl group, but in all cases the product was 1-morpholino-2-nitrobutane.

Reduction: The tin and hydrochloric acid method failed to yield a product. After reduction the nitro compound was precipitated from the acid solution by dilution with water, thus the hydrogen sulfide method of precipitating the tin salts had to be abandoned. In all experiments, the unreduced nitro compound was recovered in large quantities, indicating that reduction was not attained.

Hydrogenation with Raney nickel: Fifteen grams of 1,3-di-(4'-morpholino)-2-nitro-2-methylpropane was suspended in 190 cc. of 95 percent ethyl alcohol. Eight grams of Raney nickel was added and the bottle was connected to the Parr Hydrogenator. After the bottle was evacuated, it was then

connected to the hydrogen tank and shaken until the pressure gauge indicated a constant reading.

	Start	End
Time	10:50	11:35
Pressure	49.5 lbs.	35.3 lbs.
Temperature	28.0°	28.1°

Three hours later the pressure was the same. The bottle was disconnected. A clear solution instead of the original suspension indicated that reduction had taken place. After the Raney nickel had been filtered off and the alcohol removed, the product was distilled. At 1 mm., 7.5 grams of a colorless oil boiling at 148-150° was collected. The yield of amine was 56 percent.

Analysis for nitrogen: Kjeldahl.

	Weight of Sample	0.1000N HCl	0.1101N NaOH	Percent of Nitrogen
I	0.3267 gms.	51.00 cc.	10.28 cc.	17.01
II	0.4454 gms.	66.00 cc.	10.50 cc.	17.11

Calculated for $C_{12}H_{25}N_3O_2$ N : 17.28

Derivatives: Dry hydrogen chloride, when passed into a benzene solution of the reduced compound, formed a hydrochloride immediately. The hydrochloride upon recrystallization from alcohol and water was a white solid which decomposed at 223-225°.

Analysis for nitrogen

	Weight of Sample	0.1000N HCl	0.1101N NaOH	Percent of Nitrogen
I	0.3121 g.	49.00 cc.	22.62 cc.	10.81
II	0.3172 g.	49.00 cc.	22.40 cc.	10.79

The calculated amount of nitrogen in the expected tri-hydrochloride is 11.91. The low values are caused by the hygroscopic nature of the hydrochloride.

Analysis for chlorine

	Weight of Sample	Weight of AgCl	Percent of Chlorine
I	0.3091 g.	0.3576 g.	28.71
II	0.2662 g.	0.3025 g.	28.25

The expected trihydrochloride contains 30.21 percent of chlorine. The hygroscopic nature of the hydrochloride eliminated them from further consideration.

Phenyl Isocyanate: To one gram of the reduced compound was added one gram of phenyl isocyanate. The mixture became warm and a white solid separated out. The mixture was cooled and washed with ligroin to remove excess phenyl isocyanate. The solid after recrystallization from 95 percent ethyl alcohol formed white crystals melting at 177-178°.

Analysis for nitrogen

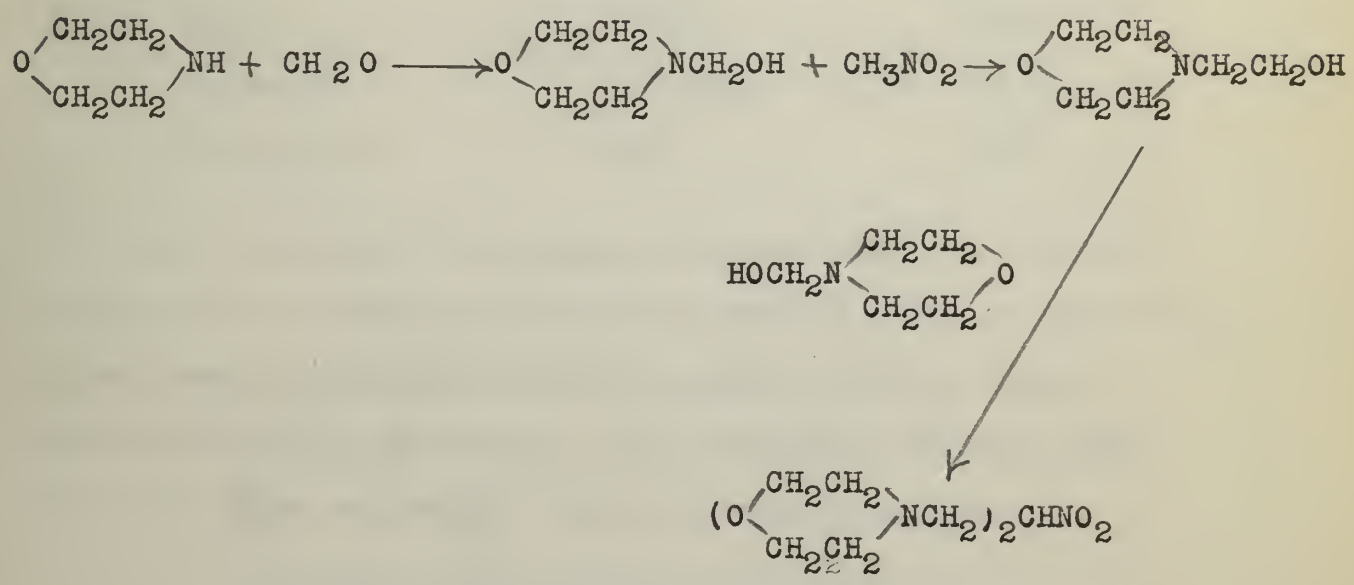
	Weight of Sample	0.1000N HCl	0.1011N NaOH	Percent of Nitrogen
I	0.3002 gms.	49.00 cc.	16.21 cc.	15.21
II	0.2866 gms.	49.05 cc.	17.82 cc.	15.17

Calculated for $C_{19}H_{30}N_4O_3$ N : 15.47

Nitromethane:

To 17 cc. (0.2 mole) of 37 percent formaldehyde and 17 cc. (0.2 mole) of morpholine, 6.1 grams (0.1 mole) of nitromethane was added. The mixture was shaken and then allowed to stand. In thirty minutes the entire mass had solidified. After filtration the weight of crude product was 25 grams. Upon recrystallization from absolute ethyl alcohol 21 grams of white needles melting at 119-120° was obtained. The following reactions are possible.

I.



II.

Unlike the reactions with nitroethane and 1-nitropropane, compound I is a primary nitro compound and is expected to react further. Thus compound II is expected with nitromethane.

Analysis of product: Kjeldahl.

	Weight of Sample	0.0981N HCl	0.1188N NaOH	Percent of Nitrogen
I	0.2413 g.	49.00	16.90	16.24
II	0.2351 g.	49.00	17.71	16.10

I	17.50
II	16.22

The yield of compound II was 81.1 percent.

Reduction:

Tin and hydrochloric acid failed completely. Hydrogenation with Raney nickel was carried out. Fourteen grams of the nitro compound was hydrogenated, using 180 cc. of 95 percent ethyl alcohol and 7 grams of Raney nickel.

	Start	Finish
Time	1:35	2:10
Pressure	49 lbs.	34 lbs.
Temperature	28°	28°

From the final mixture 10 grams of a colorless oil boiling at 161-163° at 5 mm. was collected. The oil quickly solidified in the form of beautiful white hexagonal crystals which melted at 67-68°. The product was then recrystallized from petroleum ether and dried. The yield was 80 percent.

Analysis for nitrogen: Kjeldahl.

	Weight of Sample	0.1000N HCl	0.1101N NaOH	Percent of Nitrogen
I	0.2956 g.	50.00 cc.	11.09 cc.	17.90
II	0.3212 g.	49.00 cc.	7.25 cc.	17.88

Calculated for $C_{11}H_{23}N_3O_2$ N : 18.34

Dry hydrogen chloride precipitated a hydrochloride immediately from dry benzene. The hydrochloride, after a recrystallization from 80% alcohol, was a white solid which decomposed at 232-235°.

Analysis for nitrogen

0.2620 g.	49.00 cc.	24.57 cc.	11.73

The trihydrochloride of the reduced compound contains 12.41 percent of nitrogen. The hygroscopic nature of the hydrochloride made accurate weight determinations of the samples difficult and would account for the variation between the theoretical and experimentally determined values.

Phenyl Isocyanate: To one gram of the reduced compound was added one cubic centimeter of phenyl isocyanate. The amine immediately dissolved and the mixture became warm. A white solid soon separated out. The mixture was cooled and washed with ligroin to remove excess phenyl isocyanate. The solid, after recrystallization from 95 percent ethyl alcohol, formed white crystals melting at 233-234°.

Analysis for nitrogen

	Weight of Sample	0.1000N HCl	0.1011N NaOH	Percent of Nitrogen
I	0.2630 g.	49.00 cc.	19.50 cc.	15.61
II	0.2692 g.	49.00 cc.	18.61 cc.	15.70

Calculated for $C_{18}H_{28}N_4O_3$ N : 16.09

Table V

	Yield %	M. P.	B. P. °C. mm.	Nitrogen Calcd.	% Found
$\left(O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2\right)_2CHNO_2$	81	119-120°		16.22	16.17
$\left(O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2\right)_2CNO_2CH_3$	70	124-125°		15.38	15.00
$O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2CHNO_2C_2H_5$	68		134-136 (15)	14.89	14.69
$\left(O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2\right)_2CHNH_2$	80	67-68°		18.34	17.90
$\left(O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2\right)_2CNH_2CH_3$	56		148-150 (1)	17.28	17.06
$O\begin{matrix}CH_2CH_2\\CH_2CH_2\end{matrix}NCH_2CHNH_2C_2H_5$	51		102-104 (14)	17.72	16.90

Summary

1. Morpholine and formaldehyde have been condensed with nitromethane, nitroethane, and 1-nitropropane. The condensation products have been isolated and identified in each case.

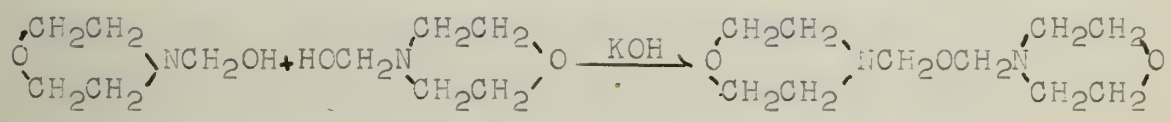
2. The condensation products have been reduced with hydrogen and Raney nickel to yield the corresponding amines.

3. Two morpholinomethyl groups are substituted in nitromethane and nitroethane. Only one morpholinomethyl group can be introduced in 1-nitropropane. The results confirm Henry's results with nitromethane and nitroethane, and Cerf de Mauny's work with 1-nitropropane. Cerf de Mauny's rule holds for nitromethane and nitropropane, but does not apply to nitroethane.

VI. 4-MORPHOLINEMETHANOL

A) Reaction of 4-Morpholinemethanol with potassium hydroxide

Henry (27) reported that $\begin{matrix}CH_3\\H\end{matrix}\!>\!NCH_2OH$ on contact with solid potassium hydroxide yielded $CH_3N{=}CH_2$. This dehydration suggested the possibility of the following reaction with a secondary amine:

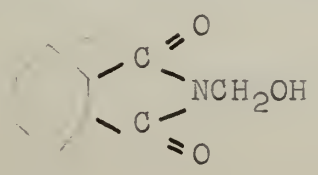


Two-tenths mole of morpholine (17.4 grams) and 17 cc. of 37 percent formalin were mixed together with cooling. Ten grams of potassium carbonate was added and the mixture was shaken. After one-half hour the upper layer of 4-morpholinemethanol was separated and dried over potassium carbonate. Pellets of sodium hydroxide were added to the 4-morpholinemethanol which was then allowed to stand for two days at room temperature. An upper layer separated. The mixture was extracted with four 40 cc. portions of ether, the ether layers were dried over potassium carbonate, and the ether was removed on a steam-bath. After all the ether was removed, 10 grams of a colorless oil boiling at 120-122° at 12 mm. was collected. The neutral equivalent was found to be 94. The oil was identified to be dimorpholinomethane. The yield of dimorpholinomethane was 53.8 percent. The formation of dimorpholinomethane may be ascribed to the partial hydrolysis of 4-morpholine-

methanol to morpholine and formaldehyde. The free morpholine can react with 4-morpholinemethanol to form dimorpholinomethane.

B) Attempted Isolation of 4-Morpholinemethanol

Since Henry (28) reported the isolation of various α-amino alcohols, 4-morpholinemethanol was prepared according to Binz and Pence (3) from 17.4 grams (0.2 mole) of morpholine and 17 cc. of 37 percent formalin. Upon distillation decomposition occurred. The previous experiment indicated that any attempt at concentration or dehydration by potassium hydroxide produced dimorpholinomethane. Potassium carbonate serves to remove water to some extent but can not remove water completely. Stewart and Bradley (51) doubted that Henry had isolated α-amino alcohols in the pure state. It appears that α-amino alcohols can exist in solution but attempts at distillation or dehydration destroy the identity of the α-amino alcohol. One exception has been noticed in the literature. Sachs (48) reported the isolation of N-hydroxymethyl phthalimide.



The compound formed from equivalent quantities of formaldehyde and phthalimide was a solid melting at 139-140°. The stability of this substituted methanol may be ascribed

to phthalimide which is itself a solid. The ordinary secondary amines are liquids which form unstable liquid substituted methanols.

VII. MORPHOLINE, FORMALDEHYDE, AND AMINES

Henry (27) prepared amino substituted methanols and reported that all the alcohols prepared reacted with secondary amines to split off water.

$$R_2NCH_2OH + HNR'_2 \longrightarrow R_2NCH_2NR'_2 + H_2O$$

No mention of aromatic secondary amines was recorded. An investigation of the differences in the reaction of primary, secondary, and tertiary amines was thus undertaken.

Experimental:

Materials: All the amines were practical grade Eastman Kodak preparations. All were redistilled before use. The morpholine was a Carbide and Carbon Chemicals Corp. preparation. The fraction boiling at 126-128° was used in the following experiments.

Titration of 4-Morpholinemethanol

To 18 cc. of 37 percent formaldehyde was added 17.4 grams (0.2 mole) of morpholine with cooling. Five grams of potassium carbonate was added and the mixture was shaken. The upper layer of 4-morpholinemethanol was then separated and titrated with hydrochloric acid to a methyl orange end point.

	5.8680N HCl
#1	32.40 cc.
#2	32.38 cc.

The acid (32.40 cc.) represents 0.1901 equivalents or 95 percent of the original morpholine (0.2 equivalents). Since 4-morpholinemethanol was prepared in the same manner in all experiments, the yields were based on the 95 percent of morpholine separated by the potassium carbonate treatment.

Primary Amines

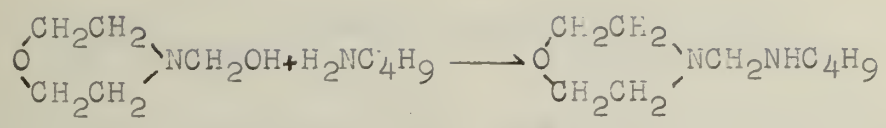
n-Butylamine:

To 18 cc. of 37 percent formaldehyde was added 17.4 grams (0.2 mole) of morpholine with cooling. Five grams of potassium carbonate was added and the mixture was shaken. The upper layer of 4-morpholinemethanol was then separated. To the 4-morpholinemethanol cooled in an ice bath was added 14.8 grams (0.2 mole) of n-butylamine. Five grams of potassium carbonate was added and the mixture was put away at room temperature for twenty-four hours. The lower water layer was separated and the upper layer was fractionated. The following fractions were collected.

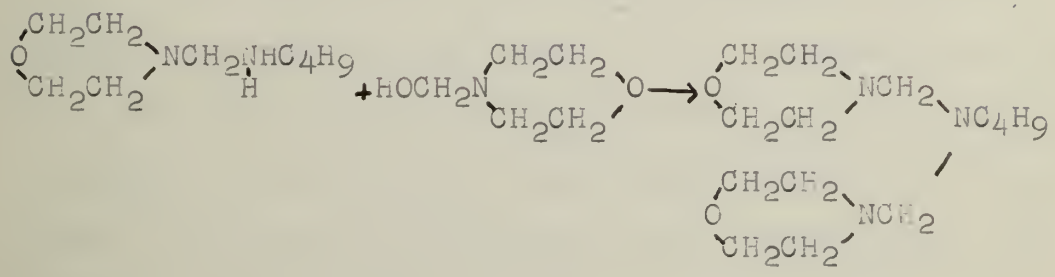
Fraction	B.p., °C	(Mm)	Weight g.	Neutral Equivalent
I	58-62	(13)	7.0	86.7
II	62-124	(13)	0.5	----
III	124-126	(13)	11.0	92.6

Fraction II was discarded since it was obviously a mixture of I and III. The following reactions with butylamine are

possible:



(equivalent wt. = 86)

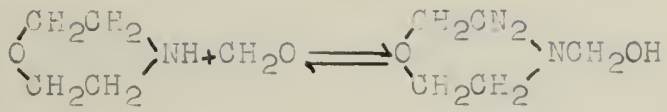


(equivalent wt. = 90.3)

Di-morpholinomethyl n-butylamine was an expected product, for morpholinomethyl n-butylamine theoretically should behave as a typical secondary amine. Fraction III was actually proven to be dimorpholinomethane (theoretical equivalent weight 93). The boiling point, equivalent weight, and rate of formation of the picrate paralleled that of known samples of dimorpholinomethane. Eleven grams of dimorpholinomethane represents a conversion of 59.2 percent of morpholine into dimorpholinomethane. The equivalent weight of Fraction I suggested the formation of morpholinomethyl n-butylamine. The 59.2 percent yield of dimorpholinomethane accounts for the formation of morpholinomethyl n-butylamine instead of di-morpholinomethyl n-butylamine.

4-Morpholinemethanol may involve the following

equilibrium.

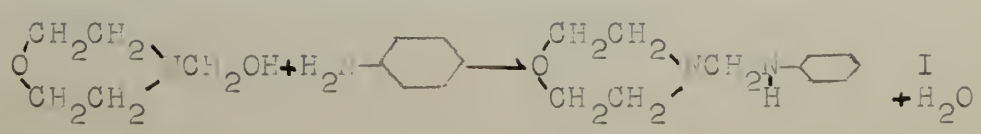


Under the conditions of the experiment the equilibrium may be shifted to the left. The free morpholine formed unites immediately with the methanol to form dimorpholinomethane. This reaction removes available 4-morpholinemethanol from reacting with morpholinomethyl n-butylamine also formed along with dimorpholinomethane. This explanation also indicates that 4-morpholinemethanol reacts much more quickly with a secondary amine than with a primary amine. The yield of morpholinomethyl n-butylamine was 20.3 percent.

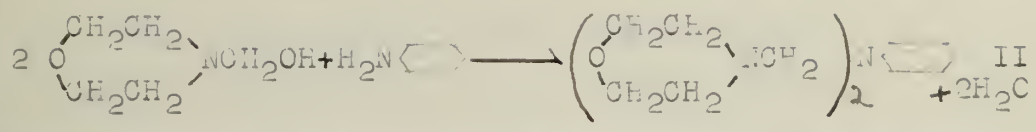
Aromatic:

Aniline

To 4-morpholinemethanol prepared from 17.4 grams of morpholine was added 18.6 grams (0.2 mole) of aniline. Five grams of potassium carbonate was added and the mixture was put away for twenty-four hours. The upper layer was then fractionated. At 108-112° (10 mm.) 20 grams of a colorless viscous oil was collected. The product when mixed with benzaldehyde remained liquid for three days. Aniline and benzaldehyde yielded the benzal derivative in five minutes. This reaction suggested the disappearance of the free NH_2 group in aniline.



The following reaction is also possible:



II

A molecular weight determination (18) was performed in order to distinguish between I and II.

Wt. of solute	Wt. of benzene	Molal depression of benzene	Observed lowering of freezing point
.3143 grams	23.9752	5.12	.346

$$\text{Molecular wt.} = \frac{1000 \times 5.12 \times .3143}{23.9752 \times .346} = 193.9$$

The molecular weight of I is 192; of II, 291. The determination suggested the formation of I. The yield was 52.3 percent.

Analysis

Kjeldahl

Wt. of sample	.09827N HCl	.1179N NaOH	% Nitrogen
.2875 g.	49.00 cc.	15.82 cc.	14.37
.2355 g.	49.00 cc.	20.30 cc.	14.40
Calculated for $C_{11}H_{15}ON_2$			14.58

Derivatives;

Picrate: The product formed a picrate melting at 147-148°. A mixed melting point determination with morpholine picrate showed no depression. The picrate

formed was morpholine picrate.

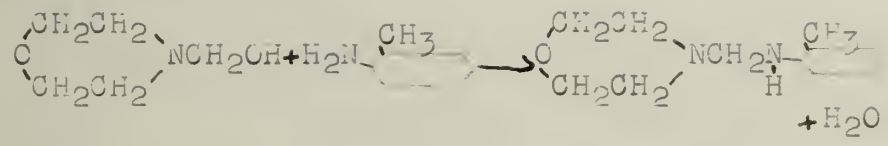
Benzenesulphonyl derivative: To 20 cc. of 20 percent sodium hydroxide was added 2 cc. of benzenesulphonyl chloride and 1 cc. of the product. After the mixture was shaken vigorously for five minutes, a white precipitate appeared. The mixture was filtered and the precipitate was recrystallized from 95 percent ethyl alcohol. White crystals (M. P. 118-120°) were obtained. When the filtrate was acidified white crystals came down. The crystals after recrystallization from 95 percent ethyl alcohol melted at 110-112°.

The benzenesulphonyl derivatives of pure aniline and pure morpholine were prepared. The aniline derivative melted at 111-112°; the morpholine derivative, at 119-120°. Since the N-morpholinomethyl aniline contains the $>NCH_2N<$ system which is unstable, hydrolysis to form morpholine and aniline is not unexpected. The precipitate insoluble in sodium hydroxide suggested the derivative of a secondary amine (morpholine) and the crystals precipitating from the alkaline filtrate upon acidification suggested a primary amine (aniline). The melting points show conclusively that hydrolysis occurred.

O-Toluidine

To 4-morpholinemethanol prepared from 17.4 grams of morpholine was added 21.4 grams (0.2 mole) of o-toluidine.

The mixture was shaken and put away for twenty-four hours. The bottom layer was then separated and fractionated. At 107-109° (10 mm) 16 grams of a viscous, colorless oil was collected. A reaction similar to that with aniline was expected.



Analysis

Kjeldahl

Wt. of sample	.09827N HCl	.1025N NaOH	% Nitrogen
.3091 g.	49.00 cc.	18.12 cc.	13.40
.3494 g.	49.00 cc.	14.30 cc.	13.42
Calculated for $C_{12}H_{18}ON_2$			13.59

The yield of product was 38.8 percent. The oil formed morpholine picrate (M. P 147-148°), showing the ease of hydrolysis characteristic of the $>NCH_2N<$ system.

Secondary Amines

Morpholine:

4-Morpholinemethanol was prepared as described previously from 9 cc. of 37 percent formaldehyde and 8.7 grams (0.1 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 8.7 grams (0.1 mole) of morpholine. The mixture immediately became warm. Potassium carbonate (5 grams) was added and the mixture was put away over-night. The upper layer was then separated and distilled.

At 12 mm. 11.2 grams of a colorless oil boiling at 122-124° was collected. The oil when titrated with .1N HCl to a methyl orange end-point had a neutral equivalent of 94.0. The yield of dimorpholinomethane was 63.4 percent.

Analysis for nitrogen

Wt. of sample	.09827N HCl	.1011N NaOH	% Nitrogen
.1555 g.	49.00 cc.	31.00 cc.	15.13
.3413 g.	49.00 cc.	11.10 cc.	15.15

Calculated for $C_9H_{18}N_2O_2$ N 15.05

The product formed a picrate melting at 146-147°. The picrate when mixed with morpholine picrate (M. P. 146-148°) still melted at 146-147°. Dimorpholinomethane must be hydrolyzed in the presence of picric acid and the derivative formed is morpholine picrate.

Piperidine:

4-Morpholinemethanol was prepared from 18 cc. of 37 percent formaldehyde and 17.4 grams (0.2 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 17.0 grams (0.2 mole) of piperidine. Five grams of potassium carbonate was added, the mixture was shaken and put away over-night at room temperature. The lower water layer was removed and the upper layer was distilled. At 12 mm., 23.2 grams of a colorless oil boiling at 111-113° was collected. The oil had a neutral equivalent of 91.6. The yield of N-morpholinomethyl

piperidine was 66.4 percent. Ten drops of the oil were mixed with 10 cc. of a saturated alcoholic picric acid solution . No precipitate appeared even after standing for one week.

Analysis for nitrogen

Wt. of sample	.09827N HCl	.1025N NaOH	% Nitrogen
.4039 g.	50.00 cc.	4.82 cc.	15.32
.2144 g.	49.00 cc.	24.13 cc.	15.29

Calculated for $C_{10}H_{20}N_2O$ N 15.22

Diethylamine:

4-Morpholinemethanol was prepared as previously described from 18 cc. of 37 percent formaldehyde and 17.4 grams (o.2 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 14.6 grams (0.2 mole) of diethylamine. Five grams of potassium carbonate was added, the mixture was shaken and put away for two days at room temperature. The layers were separated and the top layer was fractionated. The following fractions were collected.

Fraction	B.p., °C	Mm	Weight g.	Neutral Equivalent
I	86-89	(13)	20.8	84.1
II	89-120	(13)	0.8	-----
III	120-123	(13)	4.0	92.4

Fraction I was obviously the desired product, N-morpholinomethyl diethylamine (theoretical equivalent wt. 86). The

yield was 63.7 percent. Fraction III proved to be dimorpholinomethane. The yield of dimorpholinomethane was 21.5 percent. Fraction II was considered to be a mixture and was not titrated.

Analysis of Fraction I for nitrogen

Wt. of sample	0.09827N HCl	0.1011N NaOH	% Nitrogen
0.1632 g.	49.00 cc.	28.60 cc.	16.50
0.2803 g.	50.00 cc.	15.88 cc.	16.52

Calculated for $C_9H_{20}N_2O$ N = 16.28

Di-n-butylamine

4-Morpholinemethanol was prepared from 18 cc. of 37 percent formaldehyde and 17.4 grams (0.2 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 25.8 grams (0.2 mole) of di-n-butylamine. Ten grams of potassium carbonate was added, the mixture was shaken and put away at room temperature for two days. The upper layer was then removed and fractionated. At 14 mm., 25.1 grams of a colorless oil boiling at 134-136° was collected. The equivalent weight was determined to be 112.0 (theoretical equivalent weight of N-morpholinomethyl di-n-butylamine is 114). The yield of N-morpholinomethyl di-n-butylamine was 58 percent. No dimorpholinomethane was obtained as in the diethylamine experiment.

Analysis for nitrogen

Wt. of sample	0.09827N HCl	0.1011N NaOH	% Nitrogen
0.2634 g.	49.00 cc.	25.45 cc.	11.92
0.3080 g.	49.00 cc.	21.35 cc.	12.11

Calculated for $C_{13}H_{28}N_2O$ N = 12.28

Di-cyclohexylamine:

4-Morpholinemethanol was prepared from 18 cc. of 37 percent formaldehyde and 17.4 grams (0.2 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 36 grams (0.2 mole) of dicyclohexylamine. Five grams of potassium carbonate was added and the mixture was put away at room temperature for twenty-four hours. The top layer was then removed and distilled. At 8 mm., 34.2 grams of a colorless oil boiling at 112-116° was collected. The equivalent weight of the oil was determined to be 138.6 (theoretical equivalent weight of N-morpholinomethyl dicyclohexylamine is 140). The yield of N-morpholinomethyl dicyclohexylamine was 64.3 percent.

Analysis for nitrogen

Wt. of sample	0.09827N HCl	0.1011N NaOH	% Nitrogen
0.5234 g.	60.00 cc.	20.88 cc.	10.12
0.2525 g.	49.00 cc.	30.57 cc.	9.61

Calculated for $C_{17}H_{32}N_2O$ N = 10.00

Methylaniline:

To 4-morpholinemethanol prepared from 18 cc. of

37 percent formaldehyde and 17.4 grams (0.2 mole) of morpholine was added with cooling 21.4 grams (0.2 mole) of methylaniline. Five grams of potassium carponate was added and the mixture was put away at room temperature for twenty-four hours. The upper layer was then separated and fractionated. The following fractions were collected.

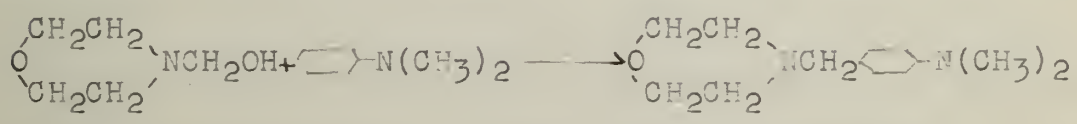
Fraction	B.p., °C	Mm	Neutral Equivalent	Weight g.
I colorless	119-124	(9)	95	3.5
IIyellow	124-140	(9)	96	6.1
III yellow	140-150	(9)	96	7.2
IV yellow	150-160	(9)	96	4.5

Fraction I had a neutral equivalent of 95. The neutral equivalent, boiling point and formation of the picrate (M. P. 146-147) showed that the product was dimorpholinomethane. Fraction I represented a conversion of 18.8 percent of the original morpholine into dimorpholinomethane. Fractions II, III, and IV were refractionated but a complex mixture boiling from 124-160° at 9 mm. was obtained. No pure compound could be isolated. This reaction indicated a sharp difference in the reaction of aliphatic secondary amines and aromatic secondary amines with 4-morpholinemethanol. With aliphatic secondary amines the expected methylene diamine was obtained in greater than 50 percent yields. With methylaniline the

expected methylene diamine could not be isolated.

Tertiary Amines

4-Morpholinemethanol and tertiary aliphatic amines do not react for the amine has no available hydrogen with which to split out water with 4-morpholinemethanol. With tertiary aromatic amines the following reaction appeared possible because of the ease with which the OH separates from amino methanols.



Experiment #1

4-Morpholinemethanol was prepared from 18 cc. of 37 percent formaldehyde and 17.4 grams (o.2 mole) of morpholine. To the 4-morpholinemethanol cooled in an ice-bath was added 24.2 grams (0.2 mole) of dimethylaniline. Potassium carbonate (5 grams) was added and the mixture was put away for twenty-four hours. The dimethylaniline appeared to form a separate upper layer. The mixture was refluxed for one hour and was again put away for two days. The upper layer was separated and distilled. The entire layer distilled at 81-84° at 14 mm. A sample of pure dimethylaniline distilled at 80-82° at 14 mm. The distillation indicated that little or no reaction had occurred.

Experiment #2

To 4-morpholinemethanol prepared from 17.4 grams of morpholine and 24.2 grams of dimethylaniline (0.2 mole)

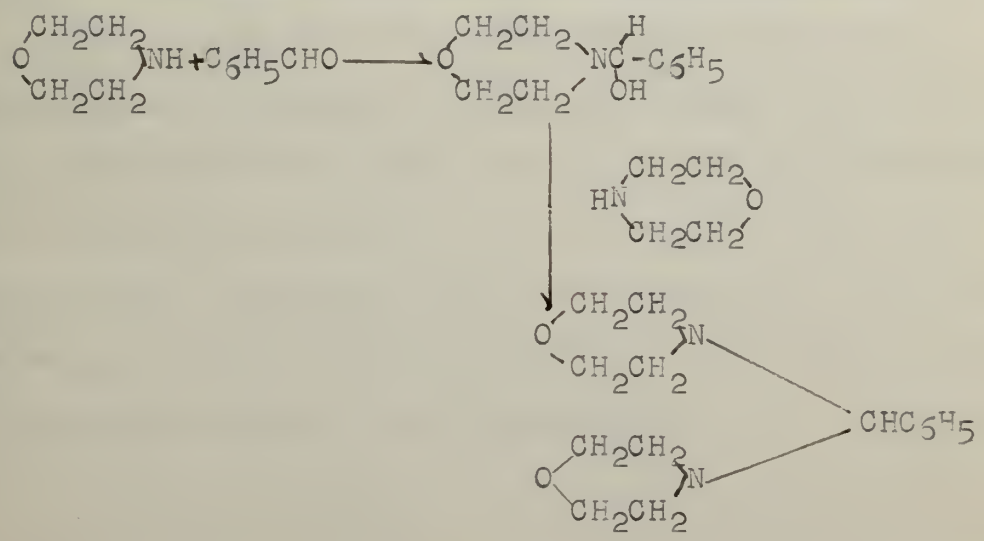
was added 2 cc. of acetic anhydride. The mixture was worked up as in the previous experiment. Unreacted dimethylaniline was recovered quantitatively.

Experiment #3

The work of Fierz-David and Blangey (14) suggested the use of sulfanilic acid as a catalyst.

To 4-morpholinemethanol prepared from 17.4 grams of morpholine and 24.2 grams of dimethylaniline (0.2 mole) one gram of sulfanilic acid was added. The mixture was stirred for four hours. The upper layer was then removed and distilled. At 7 mm., a colorless oil distilled at 73-73°. Unreacted dimethylaniline was recovered as before.

Preparation of Phenyldimorpholinomethane



To 21.2 grams (o.2 mole) of benzaldehyde was added with cooling 17.4 grams (0.2 mole) of morpholine. The mixture became warm. Soon the clear solution became milky

and viscous. In one hour a white solid appeared. The mixture was allowed to stand at room temperature over-night and was then filtered. The filtrate contained 10 cc. of unreacted benzaldehyde. The dry crude product weighed 20.4 grams. Recrystallization from 95 percent ethyl alcohol yielded beautiful white crystals melting at 101-101.5°.

Analysis for nitrogen

Wt. of sample	0.1000N HCl	0.1011N NaOH	% Nitrogen
0.3181 g.	49.00 cc.	24.68 cc.	10.58
0.3250 g.	49.00 cc.	24.04 cc.	10.64

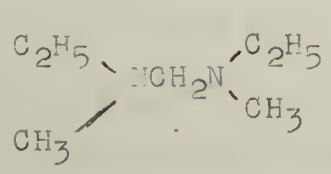
Calculated for $C_{15}H_{22}N_2O_2$ N=10.69

The product formed a picrate melting at 146-147°. A mixture of the picrate and morpholine picrate melted at 146-147°.

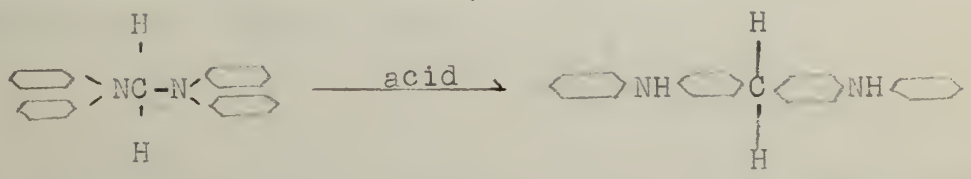
Since morpholine and benzaldehyde were used in equimolecular quantities the amino alcohol was first expected. Evidently the amino alcohol is unstable and reacts with morpholine instantly. The 10 cc. of recovered benzaldehyde indicated that only one-half of the benzaldehyde added had entered into the reaction. The yield of phenyl dimorpholinomethane was 77.9 percent.

Discussion

All the methylene diamines prepared from 4-morpholine-methanol and aliphatic secondary amines contain the system $>NCH_2N<$. This system is unstable for the presence of acids causes hydrolysis to formaldehyde and the free amines. In the attempted preparation of picrates alcoholic picric acid solutions caused hydrolysis. Graymore (23) found that



decomposes in air to form formaldehyde. Craig (11) reported that tetraphenylmethylenediamine in the presence of acid did not undergo hydrolysis but rearranged to form p, p'-dianilino-diphenylmethane



Knoevenagel (35) reported the isolation of the dihydrochloride salt of tetraethylmethylenediamine. Stewart and Bradley (51) attempted to repeat the preparation in dry alcohol and in ether. The only salt isolated was diethylamine hydrochloride. Ehrenberg (13) also reported that he was unable to obtain a dihydrochloride of the tetraethyl-methylenediamine. He, however, reported the isolation of the platinum double salt of tetraisobutylmethylenediamine. Recently Stewart and Bradley (51) claimed that all attempts

to quaternize substituted methylene diamines have failed. They claim that the iminium ion is formed in all cases. To explain hydrochloride or picrate formation the following mechanism was suggested.

$$R_2NCH_2NR_2 + 2H^+ \longrightarrow R_2N{=}CH_2^+ + R_2NH_2^+$$

iminium ion

On this basis Stewart and Bradley claim that Ehrenberg obtained not the double salt of tetraisobutylmethylenediamine but $[CH_2{=}N(C_4H_9)_2]_2PtCl_6$. The salts of the iminium ion are usually less stable than the salts of $R_2NH_2^+$. With tetraethylmethylenediamine, diethylamine hydrochloride is usually isolated. With the morpholine compounds prepared in this investigation morpholine picrate was isolated. With alkyl iodides the following mechanism was offered.

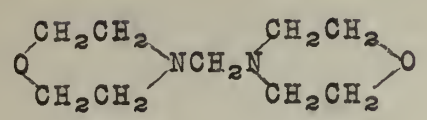
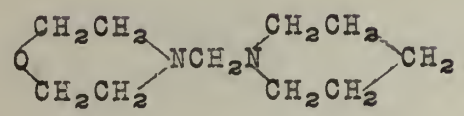
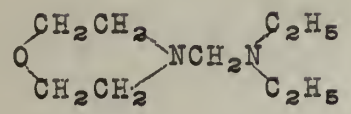
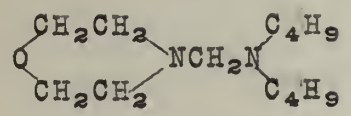
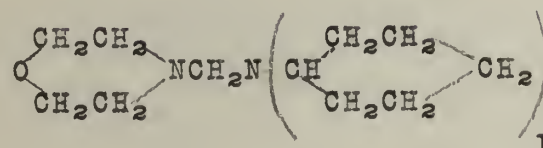
$$R_2NCH_2NR_2 + R'I \longrightarrow [R_2NCH_2\overset{+}{N}R_2R' + I^-] \longrightarrow R_2\overset{+}{N}{=}CH_2 + R_2NR' + I^-$$

Dialkylaminomethyl ethers and methylene diamines are easily hydrolyzed. In the section on morpholinomethyl ethers it was indicated that Stewart and Bradley isolated the salt of an iminium ion after much difficulty. The iminium ion explanation is the best mechanism advanced thus far and clarifies the hydrolysis phenomena of the ethers and diamines mentioned.

Phenyl dimorpholinomethane was prepared in order to see if a phenyl group substituted for hydrogen in a methylene

diamine increased the stability to hydrolysis. The compound proved to be a solid whereas all the other morpholino-methylenediamines prepared were liquids. Treatment with alcoholic picric acid, however, yielded morpholine picrate. Hydrolysis by acid was not affected by the phenyl group.

Table VI.

	B.P. °C mm.	Yield %	Neutral Equivalent Calcd.	Neutral Equivalent Found	Nitrogen, % Calcd.	Nitrogen, % Found
	122-124 (12)	63.4	93	94.0	15.05	15.14
	111-113(12)	66.4	92	91.6	15.22	15.31
	86-89(13)	63.7	86	84.1	16.28	16.51
	134-136(14)	58.0	114	112.0	12.28	12.02
	112-116(8)	64.3	140	138.6	10.00	9.86

Summary

1) 4-Morpholinemethanol and n-butylamine yielded 59 percent of dimorpholinomethane and 20 percent of morpholinomethyl n-butylamine. Aniline and o-toluidine formed the expected methylene diamines in good yields.

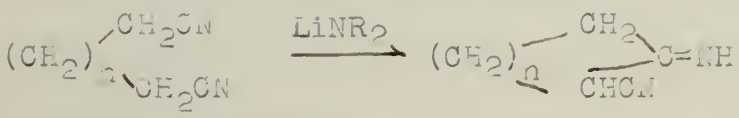
2) 4-Morpholinemethanol and aliphatic secondary amines gave good yields of the expected methylene diamine. Methylaniline yielded a small amount of dimorpholinomethane, and a complex mixture from which no pure compound could be isolated.

3) 4-Morpholinemethanol and tertiary amines did not react.

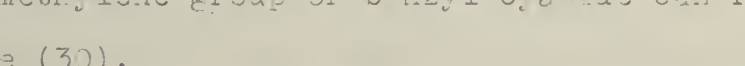
4) The methylene diamines prepared were easily hydrolyzed.

VIII. MORPHOLINE, FORMALDEHYDE, AND NITRILES

The CN group can activate hydrogen atoms linked to an adjacent carbon atom. A well-known application is Ziegler's reaction for synthesizing large carbon rings (29).



The active methylene group of benzyl cyanide can react with benzaldehyde (30).



Investigation of the reaction of 4-morpholinemethanol with benzyl cyanide was thus undertaken. Comparison of acetonitrile, propionitrile, and butyronitrile with the corresponding nitro compounds was also investigated.

Experimental

Preparation of Materials:

Acetonitrile

The acetonitrile was prepared according to the directions given by Gattermann and Wieland (17). Twenty-four grams (0.4 mole) of dry acetamide was well mixed with phosphoric pentoxide (40 grams) in a 500 cc. round-bottomed flask connected to a downward condenser. The mixture was first heated cautiously with a luminous flame. The last part of the acetonitrile was collected by heating with a

strong flame. The acetonitrile was collected, half its volume of water was added and then solid potassium carbonate was dissolved in the lower aqueous layer until the saturation point was reached. The two layers were separated. The acetonitrile (upper layer) was redistilled from a small distilling flask containing a little phosphoric pentoxide. B.P. 79-81°. Yield--10 grams.

Propionitrile

Ethyl iodide (62.4 grams) was refluxed for three hours with 32 grams of potassium cyanide in an aqueous alcoholic medium. Distillation of the mixture yielded a few drops of product. Apparently the alcohol (B.P. 78°) carried over the propionitrile (B.P. 97°) in a binary mixture. In order to increase the boiling point of the solvent the experiment was repeated using amyl alcohol and octyl alcohol as solvents. No product was isolated in either case.

Propionitrile was prepared in good yields by converting propionic acid to ethyl propionate, converting the ester to the amide and heating the amide with phosphoric pentoxide.

Ethyl propionate

One mole of propionic acid (74 grams) and two moles of absolute ethyl alcohol (92 grams) were refluxed for one hour with 50 cc. of concentrated sulfuric acid. The excess alcohol was removed on a steam-bath. The mix-

ture was then cooled and poured onto ice. The ester layer was removed and the acid layer was extracted three times with 40 cc. portions of ether. The ester combined with the ether extracts was washed with sodium bicarbonate solution and dried over anhydrous potassium carbonate. After removal of the ether 60 grams of ester boiling at 98-99° was collected.

Propionamide

Ethyl propionate (51 grams) was mixed with 80 cc. of concentrated ammonium hydroxide. The mixture, shaken twice a day, was allowed to stand at room temperature until the upper layer disappeared (seven days). The mixture was then distilled. The pure fraction boiling at 212-213° solidified upon cooling. The propionamide (20 grams) was used without further purification.

Propionitrile

Propionamide (20 grams) was mixed thoroughly with 50 grams of phosphoric pentoxide in a 500 cc. round-bottomed flask connected to a downward condenser. The mixture was heated first with a luminous flame, then with a strong flame. The propionitrile was collected, half its volume of water added and then solid potassium carbonate was dissolved in the lower aqueous layer until the saturation point was reached. The two layers were separated. The propionitrile (upper layer) was redistilled from a small distilling flask containing a little phosphoric pent-

oxide.

B.P. 96-97°. Yield--9 grams

Butyronitrile

The procedure for the preparation of propionitrile was followed.

Ethyl Butyrate

Butyric acid (176 grams), absolute ethyl alcohol (184 grams), and concentrated sulfuric acid (100 cc.) yielded 130 grams of ethyl butyrate. (B.P. 119-121°).

Butyramide

Ethyl butyrate (126 grams) and 170 cc. of concentrated ammonium hydroxide yielded 21 grams of butyramide. (B.P. 215-216°).

Butyronitrile

Butyramide (21 grams) and 60 grams of phosphoric pentoxide yielded 5 grams of butyronitrile. (B.P. 116-118°).

Benzyl Cyanide

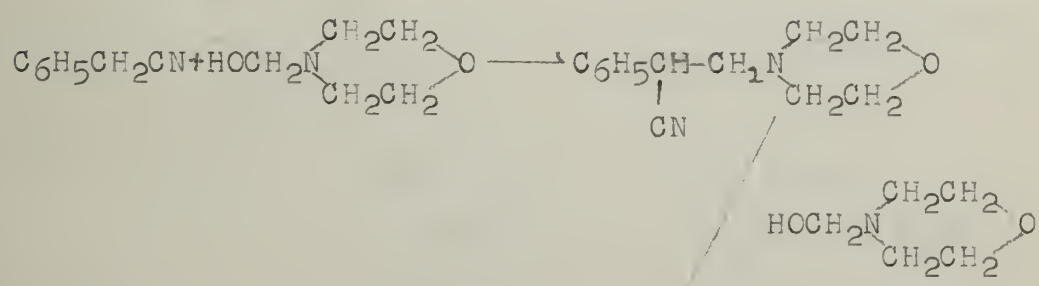
The procedure of Adams and Thal (1) was followed. A mixture of powdered sodium cyanide (26 grams) and water (23 cc.) was warmed in a 500 cc. flask fitted with a reflux condenser. When all the salt dissolved, benzyl chloride (52 grams), diluted with an equal volume of alcohol, was added slowly. The reaction was completed by heating on a steam-bath for three hours. The sodium chloride was then removed by filtration and washed with a small amount of alcohol. As much as possible of the alcohol in the fil-

trate was distilled off from a steam-bath and the benzyl cyanide in the residue was separated from the aqueous layer. The crude benzyl cyanide was distilled under reduced pressure from a "Vigreuxed" Claisen flask. At 97-101° (5 mm.) 26 grams of colorless, pure product was obtained.

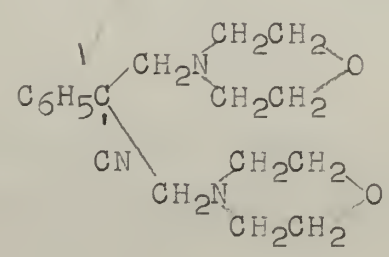
Morpholine, Formaldehyde, and Nitriles

Benzyl Cyanide

To 10 cc. of 37 percent formaldehyde was added with cooling (ice-bath) 9.2 grams of morpholine. Three grams of potassium carbonate was added and the mixture was shaken for five minutes. After twenty minutes the upper layer of 4-morpholinemethanol was separated. To the 4-morpholinemethanol was added 11.7 grams (0.1 mole) of benzyl cyanide. Three grams of potassium carbonate was added, the mixture was shaken and put away for twenty-four hours. Upon fractionating the upper layer 11 grams of a colorless oil boiling at 103-105° (7 mm.) was collected. The following reactions appeared possible.



I



II

Compound I is a secondary cyano compound. Since secondary nitro compounds do not condense with 4-morpholinemethanol, it was expected that secondary cyano compounds also would not react. Compound I was the expected product.

Equivalent wt.	Theoretical
I	216
II	157.5

found 214.1

The equivalent weight, determined by titration with 0.1 N HCl (methyl orange end-point), indicated the formation of compound I. The yield of α-morpholinomethyl α-toluonitrile was 50.9 percent.

Analysis of product

Kjeldahl

	Percent of nitrogen
I	12.96

found

Wt. of sample	.09827N HCl	.1030N NaOH	
.3159	49.00 cc.	18.90 cc.	12.75
.3000	50.00 cc.	21.15 cc.	12.77

Picrate formation

Ten drops of the product were added to 15 cc. of saturated alcoholic picric acid solution. An immediate yellow precipitate appeared. The solution was heated to boiling and was allowed to cool slowly. The precipitate was filtered off and recrystallized from 95 percent ethyl

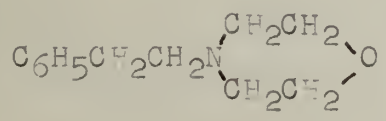
alcohol. The crystals melted at 146-148°. The melting point suggested morpholine picrate (see page 21). A mixed melting point with freshly prepared morpholine picrate showed no depression.

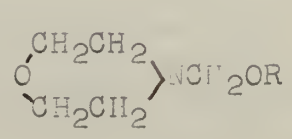
Analysis of the picrate

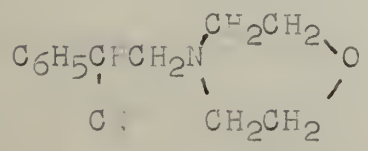
Kjeldahl

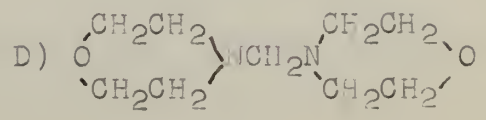
Wt. of sample	0.09827N HCl	0.1030N NaOH	percent of nitrogen
0.2390	49.00 cc.	17.70 cc.	17.53
0.3274	49.00 cc.	6.90 cc.	17.55
Calculated for morpholine picrate			17.72

The hydrolysis of the product by alcoholic picric acid was unexpected. In part I (page 40), β-phenethyl morpholine was prepared from benzyl magnesium chloride and morpholinomethyl ethyl ether. β-Phenethyl morpholine formed a stable picrate melting at 166-167°.

A) 

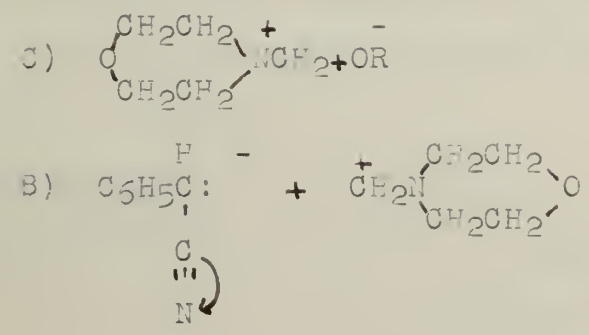
C) 

B) 

D) 

A forms a picrate readily but the introduction of a CN group as in B renders the compound susceptible to hydrolysis. B, C, and D are similar in that all are easily hydrolyzed. All form morpholine picrate. Since the ease

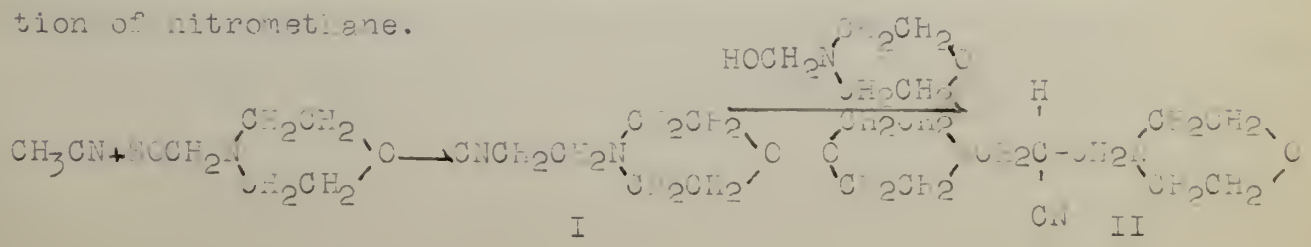
of hydrolysis increases with increasing polarity, the CN group must greatly increase the polar character of B. C is polar because of the onium tendencies of the nitrogen. B may be polar because the CN group, known to be electron-attracting (21), accumulates a negative charge at the CN end of the molecule by a mesomeric shift.



Acetonitrile

One-tenth mole of 4-morpholinemethanol was prepared from 10 cc. of 37 percent formaldehyde and 9.2 grams of morpholine. To the 4-morpholinemethanol was added 4.1 grams (0.1 mole) of acetonitrile. Three grams of potassium carbonate was added, the mixture was shaken and put away for twenty-four hours. Upon fractionating the upper layer 7.5 grams of a colorless oil boiling at 109-111° (6 mm.) was collected.

Acetonitrile was expected to parallel the reaction of nitromethane.



Equivalent Weight	Theoretical
I	140
II	119.5
found 93.9	

The equivalent weight suggested II but the equivalent weight and boiling point suggested the possibility of the formation of morpholinomethane (equivalent wt. --93; B.P. 122-124° (12 mm.)).

Analysis of product

Kjeldahl	Theoretical percent of nitrogen
I	20.00
II	17.57
found	

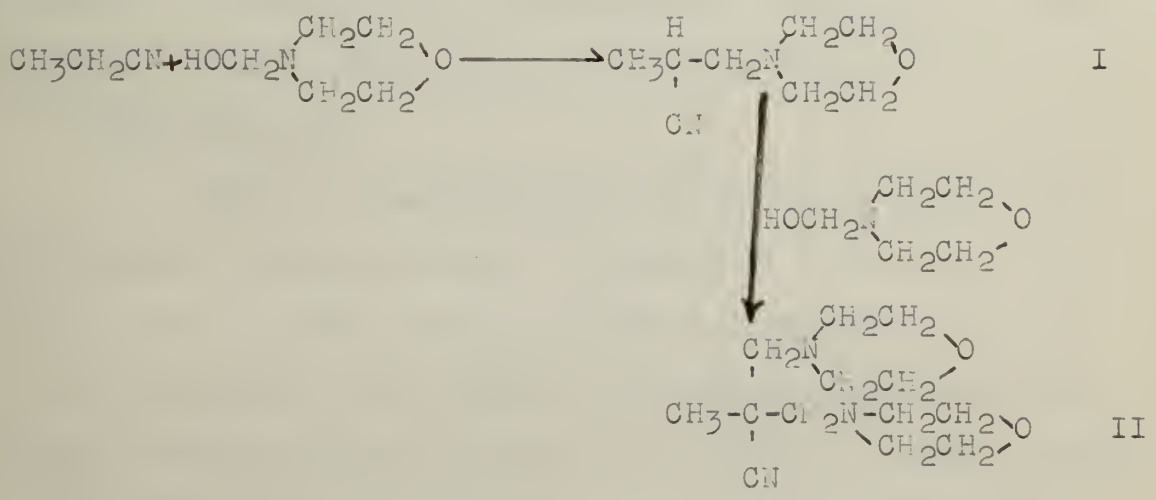
Wt. of sample	0.09827N HCl	0.1030N ~~HCl~~ NaOH	
0.2753	49.00cc.	19.45cc.	14.30
0.3206	49.00cc.	14.85cc.	14.35
Calculated for dimorpholinomethane			15.05

Picrate Formation

The product formed a picrate melting at 146-148°. Mixed melting point determinations and nitrogen analyses showed that the compound was morpholine picrate. The hydrolysis phenomena is characteristic of dimorpholinomethane.

Propionitrile

4-Morpholinemethanol was prepared from 10 cc. of 37 percent formaldehyde and 9.2 grams of morpholine. To the morpholinomethanol was added 5.5 grams (0.1 mole) of propionitrile. Three grams of potassium carbonate was added, the mixture was shaken and put away for twenty-four hours. Upon preparation of the upper layer and fractionation 7.3 grams of a colorless oil boiling at 119-121° (10 mm.) was collected.



I

II

Equivalent Weight	Theoretical
I	154
II	126.5
found 100	

Analysis

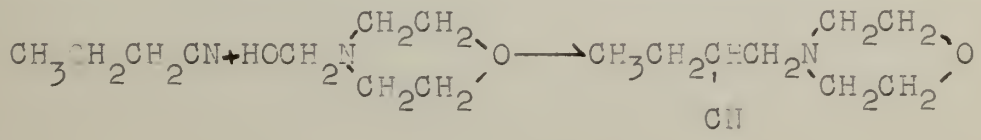
Kjeldahl	percent of nitrogen
I	18.18
II	16.60
Calculated for dimorpholinomethane	15.05

Wt. of sample	0.9827N HCl	.1030NaOH	
.3021	49.00 cc.	16.50 cc.	14.44
.3001	49.00 cc.	16.70 cc.	14.42

The product when added to saturated alcoholic picric acid formed morpholine picrate. Boiling point and analyses of the product indicated the formation of dimorpholinomethane. It is interesting to note that the same weight of product was obtained in the acetonitrile and propionitrile experiments (9.2 grams of morpholine used in each case). The yield of dimorpholinomethane was 79 percent.

Butyronitrile

4-Morpholinemethanol was prepared from 5 cc. of 37 percent formaldehyde and 4.5 grams of morpholine. To the 4-morpholinemethanol was added 2.1 grams (0.03 mole) of butyronitrile. Two grams of potassium carbonate was added, the mixture was shaken and put away for twenty-four hours. The upper layer was separated and fractionated. At 118-121° (10 mm.) 2.5 grams of a colorless oil was collected.



equivalent wt. 168

The equivalent weight was found to be 100. A Kjeldahl determination showed 14.50 percent of nitrogen. The product formed morpholine picrate.

It is clear that the same product was formed in the

acetonitrile, propionitrile, and butyronitrile experiments. Analyses, equivalent weights, and boiling point show that dimorpholinomethane is the product formed in each case. The nitriles do not enter into the reaction at all. Failure of a reaction to occur with the three simplest aliphatic nitriles indicates that the CN group is not as strong an activating group as the nitro group. The fact that a reaction occurred with benzyl cyanide shows that while a CN group does not activate the hydrogen on an adjacent methylene group in the reaction with 4-morpholinemethanol, the presence of a CN group plus a phenyl group is sufficient to cause activation of an adjacent methylene group.

Summary

1) Acetonitrile, propionitrile, and butyronitrile do not undergo a reaction with 4-morpholinemethanol. This indicates that the CN group is not as strong an activating group as the nitro group.

2) Benzyl cyanide and 4-morpholinemethanol react to form α-morpholinomethyl α-toluonitrile.

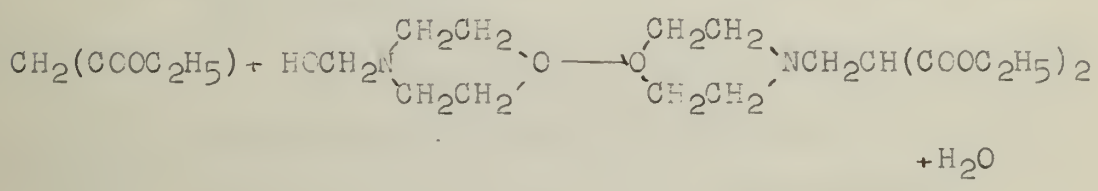
3) A CN group and a phenyl group connected to a methylene group activate the hydrogen of the methylene group.

IX. MORPHOLINE, FORMALDEHYDE, AND

A) ETHYL MALONATE

B) ETHYL CYANOACETATE

Malonic ester undergoes many reactions which depend on the reactive hydrogen atoms of the methylene group. The following reaction, analogous to the reaction with nitro compounds, was expected with 4-morpholinemethanol.



Since benzyl cyanide was shown to condense with 4-morpholinemethanol (previous section), the effect of replacing the phenyl group by a carbethoxy group was investigated in the reaction with ethyl cyano acetate.

A) Ethyl Malonate

To 4-morpholinemethanol prepared from 9.2 grams of morpholine was added 16.0 grams (0.1 mole) of ethyl malonate. Three grams of potassium carbonate was added and the mixture was put away for twenty-four hours. The upper layer was separated and distilled. At 7 mm. decomposition occurred. No product was isolated.

B) Ethyl Cyanoacetate

Experiment #1

To 4-morpholinemethanol prepared from 9.2 grams of morpholine was added 11.7 grams (0.1 mole) of

ethyl cyanoacetate. Upon shaking, the mixture became very warm. The reaction seemed more vigorous than that with ethyl malonate. Three grams of potassium carbonate was added and the mixture was put away for twenty-four hours. The yellow upper layer was then distilled. Immediate decomposition occurred as the residue in the distilling flask turned into a gum.

Experiment #2

In this experiment the effect of the alkaline condensing agent, potassium carbonate, was eliminated. Water was removed by the benzene method.

In a 500 cc. round-bottomed flask was placed three grams of paraformaldehyde, 11.7 grams of ethyl cyanoacetate and 30 cc. of benzene. At the boiling point 8.7 grams of morpholine (0.1 mole) in 25 cc. of benzene was added from a separatory funnel. At 68-72° a mixture of benzene and water was collected. The excess benzene was removed at 80°. Upon distillation of the residue at 10 mm. decomposition resulted. No products were isolated.

Experiments with ethyl malonate and ethyl cyanoacetate were terminated at this point. Introduction of the carbethoxy group produced decomposition of the products.

Summary

Morpholine and formaldehyde were allowed to react with various organic compounds containing an active hydrogen atom. Condensations were obtained with alcohols, aliphatic nitro compounds, amines, and benzyl cyanide.

With alcohols, 4-morpholinomethyl ethers and dimorpholinomethane were formed simultaneously. The amount of ether and dimorpholinomethane has been indicated in each reaction. The variation of yields of the ethers with primary, secondary, and tertiary alcohols has also been recorded. Six alkyl (or aralkyl) morpholines have been prepared from the ethers and Grignard reagents. 4-Morpholinomethyl ethyl ether, sodium, and chlorobenzene produced a small yield of benzylmorpholine. The ethers did not react with acetophenone or ethyl acetate.

With nitromethane, nitroethane, and 1-nitropropane the condensation products have been isolated, identified, and reduced with hydrogen and Raney nickel to yield the corresponding amines. Two morpholinomethyl groups are substituted in nitromethane and nitroethane. Only one morpholinomethyl group can be introduced in 1-nitropropane.

With aromatic primary amines and aliphatic secondary amines good yields of the expected methylene diamines were formed. N-Butylamine yielded 59 percent of dimorpholinomethane and 20 percent of morpholinomethyl n-butylamine. Methylaniline yielded a small amount of dimorpholinomethane and a complex mixture from which no pure compound could be isolated. Ter-

tiary aromatic amines did not react.

With benzyl cyanide a condensation took place but acetonitrile, propionitrile, and butyronitrile did not undergo a reaction. This indicates that the CN group is not as strong an activating group as the nitro group. A phenyl group and a CN group, however, connected to a methylene group activate the hydrogen of the methylene group.

Attempts to prepare 4-morpholinomethyl chloride were unsuccessful. More surprising was the failure of ortho and para nitrotoluene and 2,4-dinitrotoluene to undergo a reaction. According to the principle of vinylogy reactions were expected to parallel those with the aliphatic nitro compounds. With ethyl malonate or ethyl cyanoacetate no products could be isolated.

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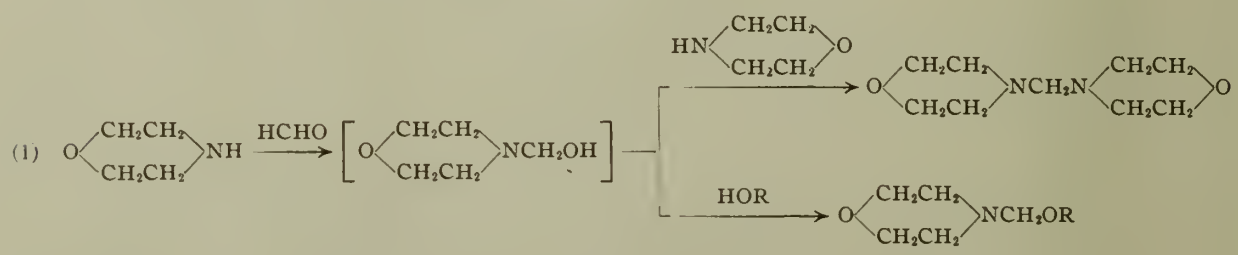
[Contribution from the Chemical Laboratories of Boston University]

4-Morpholinomethyl Alkyl Ethers and N-Substituted Morpholines

By J. Philip Mason and Morris Zief[1]

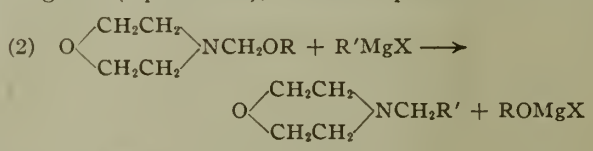
Dialkylaminomethyl alkyl ethers have been prepared by McLeod and Robinson[2] by the condensation of secondary amines with 40% aqueous formaldehyde solution and various alcohols. Stewart and Bradley[3] used paraformaldehyde instead of 40% aqueous formaldehyde solution. We have made a number of 4-morpholinomethyl alkyl ethers using the method described by Stewart and Bradley[3] with certain modifications.



It will be seen from equation (1) that there are two reactions possible when the three reactants are mixed. In order to increase the yield of the ether, we used two equivalents of alcohol to one each of morpholine and formaldehyde.

Table I shows the percentage of morpholine converted into the 4-morpholinomethyl alkyl ether and dimorpholinomethane, together with the boiling points, nitrogen analyses and neutral equivalents. Increasing yields of ether were obtained with increasing molecular weight of the primary alcohols from methyl to *n*-propyl and *n*-butyl. This may be due to the fact that the ethers obtained from higher alcohols are hydrolyzed less readily than those from lower alcohols.[2] Evidence that the hydrogen of the water split off during the formation of the ether comes from the alcohol and the hydroxyl from the hypothetical 4-morpholinemethanol is found in the lower yields of ethers obtained when secondary and tertiary alcohols were used. Picrates of these ethers could not be obtained by the usual method because all of the ethers hydrolyzed to form morpholine, and morpholine picrate was the only compound obtained.

These ethers reacted readily with Grignard reagents (equation 2), as was expected from the



work of McLeod and Robinson.[2] The results are reported in Table II.

Experimental

4-Morpholinomethyl Ethyl Ether.—Fifteen grams of paraformaldehyde (equivalent to 0.5 mole of formaldehyde), 23 g. (0.5 mole) of absolute ethyl alcohol and 100 cc. of dry benzene were placed in a 500-cc. three-necked flask which was equipped with a mercury-sealed mechanical stirrer, a separatory funnel and a fractionating column attached to a condenser for distilling the ternary mixture. The flask was heated in a water-bath kept at 85°. A mixture of 43.5 g. (0.5 mole) of morpholine and 23 g. (0.5 mole) of absolute ethyl alcohol was dropped slowly into the reaction mixture, which was stirred continuously. During this addition, which was completed in one hour

(1) This material is taken from a thesis to be submitted by Morris Zief to the faculty of the Graduate School of Boston University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

(3) Stewart and Bradley, This Journal, **54**, 4176 (1932).

TABLE I

Alcohol	% Morpholine converted to ether	% Morpholine converted to dimorpholinomethane	B. p. of ether °C.	Mm.	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found
Methyl	46.2	35.5	55.6–57	8	131	131.9	10.68	10.58
Ethyl	59.3	26.2	58–63	6	145	144.8	9.66	9.64
n-Propyl	74.0	12.0	100–102	22	159	158	8.81	8.80
Isopropyl[a]	29.7	53.6	64–66	6	159	158	8.81	8.89
n-Butyl[a]	73.8	16.3	99.5–100.5	11	171	171	8.09	8.22
Isobutyl	68.0	17.2	90.5–92.5	10	171	172	8.09	8.12
s-Butyl	58.9	34.0	92–94	10	171	170.5	8.09	8.23
t-Butyl	9.4	75.4						
Allyl	52.4	36.3	82–83	7	157	156.6	8.92	8.93
Benzyl	76.8	4.4	152–154	7	207	206	6.76	6.83

[a] Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **73**, 22 (1939).

TABLE II

N-Morpholine	B. p. °C.	B. p. Mm.	Yield, %	Neut. equiv. Calcd.	Neut. equiv. Found	Nitrogen, % Calcd.	Nitrogen, % Found	Picrate M. p. °C. (cor.)	Nitrogen, % Calcd.	Nitrogen, % Found
β-Phenethyl	147–151	13	66	191	190	7.33	7.31	166–167	13.33	13.27
α-Naphthylmethyl	185–190	9	57.7	227	225	6.17	6.00	209–211	12.28	12.40
n-Propyl	43–46	7	43.4	129	130.3	10.85	10.76	118–120	15.64	15.67
n-Hexyl	86–87	6	59.7	171	172	8.18	8.04	110–111	13.99	13.97
Benzyl	135–136.5	14	64.4	177	176.8	7.91	7.35	193.5–195	13.79	13.65

the ternary mixture of water, alcohol and benzene distilled at 65°.[4] After all of the morpholine was added, the temperature of the water-bath was raised to 100° and the remaining benzene and alcohol were distilled. The residue was transferred to a 500-cc. round-bottom flask to which was attached an efficient fractionating column. The distillate which came over up to 58° at 6 mm. pressure was discarded. The following fractions were collected.

Fraction	B. p., °C. (6 mm.)	Wt., g.	Neut. equiv.
I	58–63	26.7	144.8
II	63–110	24.3	120.5
III	110–113	4.1	97.3

Fraction I is pure 4-morpholinomethyl ethyl ether (neutral equivalent 145) while fraction III consists chiefly of dimorpholinomethane (neutral equivalent 93). If we make the reasonable assumption that fractions II and III are mixtures of the ether and dimorpholinomethane, it is possible to determine the amount of each component from the titration data and simultaneous equations. For example, 0.2546 g. of fraction II required 20.71 cc. of 0.1024 *N* hydrochloric acid for neutralization. One gram of 4-morpholinomethyl ethyl ether requires 68.36 cc. of this acid and 1 g. of dimorpholinomethane requires 104.98 cc. of this acid for neutralization. Solving the simultaneous equations

$$x + y = 0.2546$$
$$68.36x + 104.98y = 20.71$$

x equals 0.1641. Therefore 64.5% of fraction II is 4-morpholinomethyl ethyl ether. This type of analysis was used in all subsequent experiments to determine the per-

TABLE III

Alcohol used and temp. of external bath, °C.	Fraction	B. p., °C.	(Mm.)	Weight, g.	Neut. equiv.
Methyl[a]	I	55.6–57	(8)	20.0	131.9
75–80	II	57–113	(8)	8.8	127.7
	III	113–120	(8)	18.1	96.1
Propyl	I	100–102	(22)	40.9	158
87–92	II	102–128	(22)	12.7	152
	III	128–131	(22)	10.7	120
Isopropyl	I	89–93	(21)	3.9	155
80–85	II	93–98	(21)	5.8	155
	III	98–129	(21)	5.7	144
	IV	129–135	(21)	33.1	105
n-Butyl[a]	I	99.5–100.5	(11)	30.8	171
100	II	100.5–104	(11)	14.5	166
	III	104–110	(11)	8.8	158
	IV	110–122	(11)	17.3	134
Isobutyl[a]	I	90.5–92.5	(10)	29.9	172
100	II	92.5–97.5	(10)	15.1	170
	III	97.5–116	(10)	8.2	145
	IV	116–121	(10)	13.7	126
s-Butyl[a]	I	92– 94	(10)	10.3	170.5
100	II	94–100	(10)	17.0	165
	III	100–117	(10)	12.7	151
	IV	117–122	(10)	26.8	123
t-Butyl[a]	I	112–120	(11)	7.8	111
100	II	120–123	(11)	16.0	102
	III	123–125	(11)	19.5	98
Allyl[a,b]	I	82–83	(7)	10.8	156.6
100	II	83–88	(7)	12.3	153.4
	III	88–111	(7)	11.9	134.9
	IV	111–116	(7)	23.0	111.3
Benzyl[a,b]	I	140–146	(7)	6.5	173
100	II	146–152	(7)	10.8	187.4
	III	152–154	(7)	64.0	206

[a] No benzene used. Mixture was fractionally distilled after addition of morpholine was complete. First fraction was a binary mixture of the alcohol and water. [b] 0.75 mole of alcohol used.

(4) Jordan, "Technology of Solvents," Chemical Publishing Company, New York, N. Y., pp. 324–325.

centages of morpholine converted to the ether and dimorpholinomethane reported in Table I.

The other 4-morpholinomethyl alkyl ethers were made by the method described above, with the modifications given in the footnotes of Table III which summarizes all of the experimental data.

N-Substituted Morpholines.—The Grignard reagents were prepared in the usual way using 0.12 mole of magnesium and 0.12 mole of halide in 100 cc. of absolute ether. One-tenth mole of 4-morpholinomethyl ethyl ether dissolved in 50 cc. of absolute ether was then added slowly to the solution of Grignard reagent, the mixture refluxed for thirty minutes and allowed to stand overnight. The mixture was hydrolyzed with 10 cc. of concentrated sulfuric acid dissolved in 100 cc. of water. The ether layer was extracted with three 20-cc. portions of 20% sulfuric acid. Ten grams of ammonium chloride was added to the combined acid extracts to which concentrated ammonium hydroxide (about 65 cc.) was added until the solutions were alkaline. The alkaline solution was extracted with four 40-cc. portions of ether. The combined ether extracts were dried over calcium sulfate, the ether distilled and the remaining oil was distilled under reduced pressure. The results are given in Table II.

Summary

The preparation of eight new 4-morpholinomethyl alkyl (or aralkyl) ethers has been described and the amount of dimorpholinomethane formed by a competing reaction has been indicated in each preparation.

Five alkyl (or aralkyl) morpholines have been prepared from 4-morpholinomethyl ethyl ether and Grignard reagents.

BOSTON, MASS. RECEIVED MARCH 14, 1940

THE REACTIONS OF MORPHOLINE AND FORMALDEHYDE WITH ORGANIC COMPOUNDS WHICH CONTAIN AN ACTIVE HYDROGEN ATOM

Abstract of a Dissertation

Submitted in partial fulfilment of the requirements for the degree of
Doctor of Philosophy

BOSTON UNIVERSITY GRADUATE SCHOOL

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When morpholine, formaldehyde and an alcohol are mixed, the hypothetical 4-morpholinemethanol can react with the alcohol to form a 4-morpholinomethyl ether or with morpholine to form dimorpholinomethane. In order to increase the yield of the ether, equivalent quantities of morpholine and paraformaldehyde were allowed to react with two equivalents of the alcohol. In experiments with ethyl, n-propyl and iso-propyl alcohols benzene was added to remove the water formed during the reaction as part of a ternary mixture. With methyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, allyl and benzyl alcohols the first fraction distilled was a binary mixture of the alcohol and water. Increasing yields of ether were obtained with increasing molecular weight of the primary alcohols from methyl to n-propyl and n-butyl. This may be due to the fact that the ethers obtained from higher alcohols are hydrolyzed less readily than those from lower alcohols. Evidence that the hydrogen of the water split off during the formation of the ether comes from the alcohol and the hydroxyl from the hypothetical 4-morpholinemethanol is found in the lower yields of ethers obtained when secondary and tertiary alcohols were used. Picrates of these ethers could not be obtained by the usual method because all of the ethers hydrolyzed to form morpholine, and morpholine picrate was the only compound obtained.

In each experiment fractions of pure ether and mixtures of the ethers and dimorpholinomethane were collected. The weight and neutral equivalent of each fraction was recorded. From the titration data and simultaneous equations the amount of each component formed was determined. With decreasing yields of the ethers increasing yields of dimorpholinomethane were obtained. The ether and dimorpholinomethane together accounted for 80 per cent. or more of the original morpholine.

4-Morpholinomethyl ethyl ether and acetophenone were refluxed for one hour. Instead of the formation of the expected β-morpholino propiophenone, dimorpholinomethane was obtained from the reaction mixture. The acetophenone was not involved in the reaction. Hydrolysis of the ether occurred. 4-Morpholinomethyl ethyl ether when refluxed with ethyl acetate also formed dimorpholinomethane. 4-Morpholinomethyl ethyl ether, chlorobenzene and sodium were mixed in benzene. Benzylmorpholine was isolated in poor yields.

4-Morpholinomethyl ethers reacted readily with Grignard reagents to yield N-substituted morpholines. The Grignard reagents were prepared in the usual way. The 4-morpholinomethyl ether dissolved in absolute ethyl ether was added slowly to the solution of the Grignard reagent. After hydrolysis with sulfuric acid ammonium chloride and ammonium hydroxide were used in the neutralization process to keep the magnesium salts in solution. Extraction with ether yielded the desired product. In this manner benzyl chloride, α-bromonaphthalene, ethyl iodide, n-amyl chloride, tert-butyl chloride, and bromobenzene yielded β-phenethyl, α-napthylmethyl, n-propyl, n-hexyl, neopentyl, and benzyl morpholine respectively. All the N-substituted morpholines formed crystalline picrates which were analyzed.

Attempts to isolate 4-morpholinomethyl chloride or its polymer were unsuccessful. Morpholine, paraformaldehyde and dry hydrogen chloride in chloroform solution yielded morpholine hydrochloride. When the dry hydrogen chloride was replaced by thionyl chloride morpholine hydrochloride was also prepared. From morpholine hydrochloride, paraformaldehyde and thionyl chloride only morpholine hydrochloride was isolated. The instability of

4-morpholinomethyl chloride makes its isolation difficult, if not impossible.

Morpholine and formaldehyde were condensed with nitromethane, nitroethane and 1-nitropropane. With nitromethane and nitroethane, white, crystalline solids melting at 119-120° and 124-125° respectively were obtained. The nitropropane product was a liquid boiling at 134-136° at 15 mm. Equivalent quantities of morpholine, formaldehyde, and nitro compound in all cases formed the same product as two equivalents of morpholine and formaldehyde with one equivalent of nitro compound. With nitromethane and nitroethane, two hydrogen atoms were replaced by 4-morpholinomethyl groups. With nitroethane, the hydrogen atoms attached to the carbon adjacent to the nitro group were replaced. With 1-nitropropane, only one hydrogen atom linked to the carbon adjacent to the nitro group was replaced.

The three new compounds—1,3-di-morpholino-2-nitro propane, 1,3-di-morpholino-2-nitro-2-methyl propane and 1-morpholino-2-nitro butane—were reduced to the corresponding diamines with Raney nickel in a Parr hydrogenator. 1-Morpholino-2-nitro butane was also reduced in over 50 per cent. yields by tin and hydrochloric acid. 1,3-Di-morpholino-2-amino propane and 1,3-di-morpholino-2-amino-2-methyl propane formed crystalline phenyl isocyanate derivatives. 1-Morpholino-2-amino butane did not give the usual derivatives for a primary amine. 3,5-Dinitrobenzoic acid, however, yielded a solid derivative.

Morpholine and formaldehyde were condensed with o-nitrotoluene, p-nitrotoluene and 2,4-dinitrotoluene. Reactions similar to those with the aliphatic nitro compounds were expected according to the principle of vinylogy. In each experiment, however, the original reactants were recovered quantitatively.

Morpholine was added to an equivalent quantity of 40 per cent. formaldehyde. Potassium carbonate was added and the mixture was allowed to stand for thirty minutes. The upper layer of 4-morpholinemethanol was separated. Upon distillation, decomposition occurred. 4-Morpholinemethanol was put away with solid potassium hydroxide for twenty-four hours. Formation of di-morpholinomethyl ether was expected. Actually dimorpholinomethane was formed. These experiments indicate that while 4-morpholinemethanol may exist in solution, isolation by distillation or dehydration to form ethers is impossible.

4-Morpholinemethanol was prepared as described from morpholine, 40 per cent. formaldehyde and potassium carbonate. The 4-morpholinemethanol was then titrated with 5.868 normal hydrochloric acid. Ninety-five per cent. of the original morpholine was converted into 4-morpholinemethanol.

4-Morpholinemethanol was treated with primary, secondary and tertiary amines. With butylamine a 60 per cent. yield of dimorpholinomethane was obtained along with a 20 per cent. yield of N-morpholinomethyl n-butyl amine. The products show that 4-morpholinemethanol reacts more quickly with morpholine than with n-butylamine. 4-Morpholinemethanol may be in equilibrium with morpholine and formaldehyde. With aniline and o-toluidine, aromatic primary amines, better than 50 per cent. yields of the expected N-morpholinomethyl aniline and N-morpholinomethyl o-toluidine respectively were obtained.

4-Morpholinemethanol and aliphatic secondary amines in all cases formed better than 50 per cent. yields of the expected methylene diamine. Morpholine,

piperidine, dicyclohexylamine, di-n-butylamine and diethylamine were the aliphatic secondary amines investigated. Methyl aniline, an aromatic secondary amine, formed a complex mixture from which no pure product could be isolated. The product distilled continuously from 126-170 (12 mm.) with no constant fraction.

Acetic anhydride and sulfanilic acid were used as catalysts for the condensation of 4-morpholinemethanol and dimethylaniline. p-Morpholinomethyl dimethylaniline was expected but no reaction occurred. The original reactants were recovered.

All the methylene diamines were easily hydrolyzed. No stable derivatives were prepared. Picric acid resulted in the formation of morpholine picrate. From N-morpholinomethyl aniline and benzenesulfonyl chloride the benzenesulfonyl derivatives of aniline and morpholine were isolated. Phenyl dimorpholinomethane prepared from benzaldehyde and morpholine, in which a methylene hydrogen is replaced by a phenyl group, was also easily hydrolyzed.

4-Morpholinemethanol was allowed to react with acetonitrile, propionitrile and butyronitrile in the presence of potassium carbonate. In each case dimorpholinomethane was formed. The nitrile did not take part in the reaction at all. Comparison of the reaction of the simple aliphatic nitro compounds with the corresponding nitriles shows that the nitro group is a stronger activating group than the CN radical. From benzyl cyanide and 4-morpholinemethanol, however, α-morpholinomethyl-α-toluonitrile was obtained. This reaction indicates that a phenyl group and a nitrile group attached to a methylene group can activate the methylene hydrogen atoms. α-Morpholinomethyl-α-toluonitrile with saturated alcoholic picric acid formed morpholine picrate. β-Phenethyl morpholine prepared previously from benzyl magnesium chloride and 4-morpholinomethyl ethyl ether formed a stable picrate. The replacement of a hydrogen atom by a nitrile group renders the molecule more polarized, and thus more easily hydrolyzed. α-Morpholinomethyl-α-toluonitrile resembles 4-morpholinomethyl ethers and the methylene diamines in the ease of hydrolysis.

4-Morpholinemethanol was condensed with ethyl malonate and ethyl cyanoacetate. No product was isolated. Violent decomposition took place in each case upon distillation of the reaction mixture.

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